# Blackwater Fever

(Bilious Malignant Tertian Ague)

A. G. NEWELL



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To illustrate Case 4.

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(BILIOUS MALIGNANT TERTIAN AGUE)

BY

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#### London

JOHN BALE, SONS & DANIELSSON, LTD.

OXFORD HOUSE
83-91, Great Titchfield Street, Oxford Street, W.

1909

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VIELLOUISE COMMITE I

#### PREFACE.

In this little book I desire to give my experiences of Blackwater fever, and to state the conclusions I have come to regarding the nature of the condition from my observation of cases of blackwater fever and severe forms of malaria, my experience being based on nine years' work in India—practically all in the highly malarial regions of the Dooars and Terai in Bengal. It is not my intention to touch on the subject of malaria beyond what affects my views on blackwater fever. Such methods of treatment as I have advocated I have found successful in my own personal case and in those cases treated by me. To those who have not had experience of the condition known as blackwater fever—a term highly unscientific and deserving to be expunged—I trust these methods will be found as useful as I have experienced them. If the views as to the nature of the condition are not accepted by any, I trust this work will stimulate them to scientific enquiry, confirming them or otherwise. I do not believe a large number of cases alone justifies one in expounding opinions; I rather think observation of facts from a given number of cases to one man may lead to a truer interpretation of the facts observed than perhaps a very much larger number of cases would to another who either observed wrongly or interpreted falsely. I have observed the facts related herein, and I believe the interpretation I have put on them to be true. If my work arouses a greater interest in this condition (which I am much interested in), and if it proves of value to those medical officers destined to work in highly malarial districts, it will not have been written in vain.



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### BLACKWATER FEVER

(Bilious Malignant Tertian Ague).

#### CHAPTER I.

INTRODUCTION.

THE following article was inserted in *Indian Public Health*, January, 1909, as an editorial and a brief preliminary note on this subject by the author.

"Blackwater fever, or hæmoglobinuria, has of recent years come rather prominently before the Indian public owing to a number of cases in the tea districts, and its being regarded so seriously led to the appointment of a medical investigation into the nature of the malady by the Government of Eastern Bengal and Assam. Its exact nature has not been definitely agreed upon by the medical profession in general, and many theories and suggestions have been made as to its nature. Of these the following are the most important, viz.: (1) That it is a distinct disease the nature of which is unknown; (2) that it is due to a blood parasite similar to Pyrosoma bigeminum, which causes Texas fever; (3) that it is due to a tickbite; (4) that it is a quinine intoxication; (5) that it is due to some known or unknown form of the malarial parasite. With reference to the first theory, the writer can only say that what is known of the disease does not exclude its relationship to the existing affections of malaria,

and there is no reason why it should be regarded in any way as an entirely new disease. As regards theory (2), although there are analogies between Texas fever of cattle and blackwater fever yet it does not follow that the two diseases need be of the same nature, for black urine and hæmoglobinuria may be a complication of many diseases with no similarity to one another. Black urine may occur in jaundice when there is a large amount of biliverdin together with bilirubin and other varieties of black pigment. Theory (3) can be dismissed, because if anyone has ever experienced a tick-bite he usually knows it, and the writer, who has had blackwater, did not have a tick-bite. Furthermore, people can get blackwater in the Hill stations of India or in England long after they have left their malarial district. The idea that it is in any way related to kala-azar seems too absurd. If blackwater fever had any connection to kala-azar one should find the Leishman-Donovan body; besides, recovery or death would not be the invariable rule, but we should have some cases drifting into that terrible condition in which kala-azar drifts. The writer, from his experience of both diseases, has no hesitation in denouncing this theory as untenable. That it is a quinine intoxication is believed by many. Koch some time ago pointed out that when a malarial patient neglected taking his quinine, and then, when he got a bad attack of fever, suddenly took a large dose, developed blackwater fever. From this, the idea or conclusion got about that Koch said quinine produced blackwater fever. This, as can be seen from the previous sentence, was not true. On top of this many planters began rather to neglect their quinine, and I am afraid the increase of blackwater fever cases in the tea districts must be ascribed to this. That blackwater may arise in this way I have not the slightest

doubt now, though I was rather dubious at first. But that quinine produces the blackwater fever either from the mere dose or from any relation to isotonic conditions I do not believe. Many planters have taken large doses of quinine without serious effect (and large doses of quinine have been common for many years before blackwater fever cases were recognized) and yet blackwater fever was unknown. Of course, it may be said that this was due to the disease not being recognized. I am prepared to admit this, since, even now, with plain facts before us concerning this disease, we have all the above theories and different interpretations put on the symptoms. As to the view that the drug produces blackwater owing to isotonic laws, and that the sulphate does this whilst the hydrochlorate does not, I think it is quite easy to demonstrate that the latter salt will induce it as much as the former, and time will show that if the hydrochlorate were persisted in it would not make the disease disappear, if, of course, the irregularity of quinine was still persisted in. The fact, however, that blackwater fever has occurred in cases where no quinine was taken proves that quinine itself is not the causa causaus. Lastly, there is the malarial origin of the disease. The factors put forth in favour of this are: (1) That it occurs in the most malarial regions: (2) malarial parasites have been found in the cases before the development of blackwater; (3) the malarial nature is regarded from the increase in number of large mononuclear leucocytes and the presence of many pigmented such. At the present blackwater fever is regarded by most as due to malaria, but how it occurs is not definitely known or agreed upon.

"The writer regards the disease, from his experience of it and several years' experience of malaria in all its forms in the most malarial districts of India, in the

following light. He considers that it will only be found in malarial patients, and that it may be brought about by a malarial patient neglecting his quinine, and then suddenly taking a large dose, and that it may also occur in one who has regularly taken his quinine, but who has allowed his liver to become unduly congested, from some cause or from fever, and who then on top of this takes a dose of quinine. In both cases the writer considers that congestion of liver is necessary to the production of blackwater fever before the ingestion of quinine. In every case of blackwater fever there will be found antecedent to it malaria, an attack of malignant malaria fever, and a congested liver. If one considers what occurs in an ordinary malaria fever case this view of the writer's will not be difficult to understand. In the simple malaria the parasite enters the red blood corpuscles, and on reaching the maturity of its intra-corpuscular existence bursts the corpuscle when red blood colouring matter is for the most part thrown into the blood serum. It is carried to the liver, where most of it is dealt with. liver is quite able under ordinary circumstances to deal with the hæmoglobin in the benign varieties of malaria. In the malignant varieties, however, where there is greater fever and where the liver is usually congested, the liver will only be able to deal with hæmoglobin as far as its condition permits, and the writer unhesitatingly states that with the malignant varieties of malaria hæmoglobin frequently passes out in the urine, as is evidenced by its colour, and that in many cases it is difficult to know where malignant tertian malaria ends and blackwater fever begins, so far as the urine condition is concerned. The writer has seen many examples of thesewhere the symptoms were in all respect similar and only a difference in the shade of the colour of the urine exists.

Therefore his experience would lead him to believe that blackwater fever is simply malignant tertian malaria with a superadded biliary condition by which the liver is unable to deal with the hæmoglobin and, therefore, has to pass out of the system. Its following on a sudden dose of quinine can be easily explained compatible with this view of the writer. The attack of fever coming on with a highly congested liver means that the fever is likely to be a severe ague attack, and when the quinine is taken, of course, very soon the parasites are destroyed, and are expelled from the blood corpuscles with the hæmoglobin. But the liver, already congested, will be more so with this attack, and the quinine, especially if large, will further depress the action of the liver, and so the liver, being unable to deal with the condition—i.e., the sudden call on it to deal with a very large destruction of parasites, large quantity of hæmoglobin and destroyed blood corpuscles—it follows Nature must resort to some of its other excretory organs, and what more natural organ than the kidneys? Hence the hæmoglobinuria. Blackwater fever, then, is only a condition, not a disease per se, arising in a severe malignant tertian malaria in which the liver is too congested to deal with parasites, hæmoglobin and ruptured corpuscles, and which might be induced by quinine or a chill aggravating the liver condition or distressing its function. An explanation is required to fit this theory regarding its presence in some malarial quarters and not in others. The author regards this explained by the presence or absence of specially malignant tertian parasites in some districts and not in others. The prevention of blackwater consists in the prevention of tertian malaria, and if such malaria has been contracted to keep the liver relieved of congestion primarily, and secondarily avoid large doses of quinine at the time

the liver is congested. Quinine, in my opinion, should not be discontinued, and I believe smaller doses of quinine than usually taken will prevent malaria if the doses be taken regularly and at regular intervals. In all cases the liver should be free of congestion at the time—such are the views of the undersigned open to criticism.

"Blackwater fever can be produced without quinine, and no quinine intoxication alone will produce it. If quinine ever does produce black urine it certainly will not produce fever and the other symptoms of blackwater. Blackwater fever is the natural ending of all malignant tertian malaria. This is not to say that all malignant and tertian will end in blackwater fever, but that given a case of malignant tertian malaria in which no quinine is taken, after renewed attacks either the patient will die from the malignant tertian, or, if he survives a good many such untreated, blackwater fever must result. Where quinine seems to produce the attack it is more than probable that the attack would have come on in many cases even if the quinine had not been taken. In my opinion it would seem that bile pigment of a variety produces the hæmolysis.

"I have only known blackwater fever to occur in *dark-haired* persons. The only explanation I can give of this is that such persons are probably oftener attacked by mosquitoes which prefer to attack dark parts of the body—*e.g.*, ankles, head, &c." <sup>1</sup>

Definition.—Blackwater fever may be defined as an acute complication of hæmoglobinuria occurring in a

<sup>&</sup>lt;sup>1</sup>[The condition may occur in red-haired persons, and these perhaps may be regarded as the dark-haired examples of brunettes. Mosquitoes probably prefer attacking dark-haired parts of the body, as they will be less liable to attack, and instinct has possibly taught them this. At any rate, if a person wears white stockings they are less liable to be attacked at the ankles, and this supports the above view.]

patient affected with the malignant tertian parasite of malaria in whom the congestion of the liver has proceeded so far as to incapacitate the liver from dealing with the destruction of red blood corpuscles and hæmoglobin emitted therefrom, and which congestion and inactivity of the liver might be exaggerated by a sudden chill or sudden dosage of quinine. Thus hæmoglobinuria may occur as a condition in a subject with malignant tertian parasites as a result of (a) continued fever therefrom untreated, causing severe congestion of liver; (b) in a case insufficiently treated with or without quinine experiencing a chill; and (c) in a case irregularly and insufficiently treated with quinine which is suddenly treated with a moderate or large dose of quinine.

According to my view, it is only with the malignant tertian variety of the malarial parasite that the condition of blackwater or hæmoglobinuria can occur, and it is the very severe degree of congestion of the liver existing which, producing imperfectly formed biliary pigments in the blood, probably produces the hæmolysis of the red corpuscles, and which, with their contents are unable to be dealt with by the liver already incapacitated. This is not saying that the congestion of the liver is the cause of blackwater fever, for I have already said, in ordinary simple cases—all benign varieties of malaria—we also have a certain amount of congestion of the liver necessarily, but in these cases the congestion is neither so great nor does it arise so quickly as it does in the malignant tertian infection, and so, in the benign infections the liver is quite capable of dealing with the blood condition. The benign forms do not appear to be capable of giving rise to hæmoglobinuria and only in some malignant tertians does it appear to occur, and in such the condition of acute congestion of liver would appear to be a necessity.

I am of the opinion that there are degrees of malignancy of even malignant tertian infections, and this will help to explain why we should have malignant tertian infections in Bombay and Calcutta suburbs without having the condition of blackwater. I have seen malignant tertian ague outside of the Dooars and Terai, but I have never seen such severe attacks of malignant tertian outside of these highly malarial districts as I have seen therein. This is explainable on this opinion.

I am able to include here the views expressed by me at the discussion on Dr. Bentley and Captain Christophers' paper on Blackwater Fever read at the Bombay Medical Congress, February, 1909. In the few minutes allotted I said:—

"I am glad to see that both Drs. Christophers and Bentley regard Blackwater Fever as of malarial origin, and are inclined to put the blame on to the malignant tertian parasite. My experience of the disease has led me to hold the view for some time that blackwater fever is only to be found in patients who have had malignant tertian malaria. In favour of this view is: (1) That this parasite can and has been found prior to the occurrence of hæmoglobinuria; (2) that the absence of its finding when hæmoglobinuria has occurred is in accordance with the habits of the malignant tertian parasite to disappear from the peripheral blood; (3) in marked cases of blackwater fever the temperature chart is that of a malignant tertian infection; (4) the period of usual prevalence is that of the malignant tertian parasite. How does the condition of hæmoglobinuria arise? The idea of a toxin, I am glad these observers say, may be dismissed, and I would add that other observers have searched for a toxin and failed, and blood from an infected case has failed to reproduce the disease.

Quinine as the main factor in the production of the condition may also be dismissed, as it can occur apart from the taking of any quinine. That quinine bihydrochloride will have less tendency to precipitate it than the sulphate I deny, as I have had a case occur on the taking of quinine bihydrochloride, and also when quinine bihydrochloride was intramuscularly injected later the hæmoglobinuria recurred. In my opinion blackwater fever only occurs with malignant tertian parasite, and then in such infection only as a result of congestion of liver being present. The congestion of the liver, in my opinion, would appear to be a necessary condition for the condition of hæmoglobinuria to occur. In ordinary benign infections the liver is able to deal with the destroyed blood corpuscles and the hæmoglobin thrown into the plasma. But in malignant varieties the liver is highly congested, and its power to deal with the hæmoglobin is impaired, and so what more natural than that the hæmoglobin should pass out through the urine? In my opinion, in the malignant tertian infections hæmoglobin frequently passes out into the urine in small quantities not sufficient to call the case blackwater fever, and also that it is extremely difficult in some cases of malignant tertian malaria to know where malignant tertian ends and blackwater fever begins. Blackwater fever is, in my opinion, only malignant tertain fever with a superadded biliary condition, owing to which the liver is unable to deal with the hæmoglobin. This view of blackwater fever of mine is quite in accord with the so-called relation to quinine. If quinine be given in a case of malignant tertian with congested liver, the quinine further depressing the action of the liver will aggravate matters and so precipitate an attack. I am quite agreed to accept the authors' views as to the presence of an autolysin leading to the hæmoglobinuria, and I do not consider my view of blackwater fever in any way militates against their observations. In my opinion, owing to the biliary condition present, there are circulating in the blood in such cases probably imperfectly formed varieties of bile pigment, and that such pigments in some way unexplained cause the clogging of the red blood corpuscles and their solution. That bile pigment in some form does circulate in the blood in such cases no one will deny who has any experience of the disease, and there is urinary evidence of it.

"There is one point I would like to point out in connection with blackwater fever, and that is a point in its treatment. In all cases it is of the utmost importance to primarily relieve the liver congestion before giving quinine. The prevention of blackwater fever consists in the prevention of malignant tertian malaria, and in relieving the liver of any congestion in such cases before the exhibition of quinine. With regard to cassia beareana I would like to add that I have found it most useful, both in severe malignant tertian malaria and in blackwater fever. But to be of any use it must be given in doses more than double that in which it is usually given,1 2 to 4 drams three or four times a day or 1-dram doses every hour or two. I have found it has in such doses a diaphoretic, diuretic and cardiac tonic effect. It seems to have an action similar to digitalis, combined with a diaphoretic effect."

In the succeeding chapters I will elucidate these statements, expand on them briefly, and give a few illustrative cases.

<sup>&</sup>lt;sup>1</sup> The usual dose of Christy's preparation of the liquid extract of cassia beareana is 30 to 60 minims.

#### CHAPTER II.

#### SYMPTOMS OF BLACKWATER FEVER.

THE attack is invariably sudden in its onset, and demonstrates itself by a rise of temperature, usually related in severity to the degree of hæmoglobinuria, and by hæmoglobinuria. Before the attack actually comes on the patient feels "out of sorts," and anticipates an attack of "fever." There may or may not be a rigor—depending on the severity of the attack. The patient is invariably "off his feed" the day or so before the attack, and may experience sensations of nausea; at times there may be distinct retching and vomiting, and such vomit may be slightly or distinctly bile-stained. If the liver is examined, it is found distinctly congested, and the left lobe may be tender, as also the gall-bladder. The spleen, too, will be found both enlarged and tender. He will have a slight yellow tinge of the sclerotic, and, as a rule, the bowels will be found to be constipated. Examination of the blood when these premonitory warning signs are found will reveal the presence of malignant tertian parasites alone, or mixed with other varieties of the malarial organisms.

When the condition of hæmoglobinuria has occurred, there is very soon vomiting of very green or greenish

<sup>&</sup>lt;sup>1</sup> The fæces may be absolutely black in colour, or, if the degree of congestion be very acute and pigmentation of skin, &c., highly marked, they may even be clay-coloured, as in "jaundice."

yellow matter with mucus, and this vomiting may be very constant and depressing. Very little nutriment can be retained, and the patient gets seriously exhausted if permitted to continue unchecked. Intermittent retching is very frequent between actual attacks of vomiting. The liver now will be found more tender than before and larger. If an early dose of a cholagogue is given, the vomiting may be absent or much lessened. The spleen is more tender, and enlarges rapidly to various distances, even below the umbilicus. If one remains beside the patient one can very distinctly mark out the progressive enlargement of the spleen. It is owing to this enlargement of the spleen that the vomiting is in part due, by actual pressure of the enlarged spleen on the cardiac end of the stomach, and probably much of the distress during vomiting is due to the pressure on the spleen by the attack of vomiting causing pain. The spleen is not only much enlarged and congested, but it is also very tender. Even the slightest pressure on the spleen may be sufficient to elicit tenderness, as in my own case. The spleen may be so enlarged, as in my own case, that one feels compelled to lie still, as even turning of the body to the left side might give rise to uneasiness and tenderness.

With the onset of these congestions of liver and spleen there is an immediate pigmentation of the skin of a characteristic yellow-gold tinge, and the sclerotics are also markedly tinged. The patient is both anæmic and highly pigmented by deposition of bile pigment, and presents a *characteristic* appearance, quite different from the ordinary jaundice. If the bowels are moved, the fæces are frequently dark-coloured or black. There is a frequent desire to micturate, and usually 10 oz. are passed. There is thus frequent micturition, and a large

amount of urine is passed. Frequently one or both kidneys are slightly painful.

The urine is characteristic. It varies in shade from a deep sherry red to as black as ink. It always appears darker in colour when looking down upon it in the chamber-pot. The urine should always be viewed in a glass measure. Hæmoglobinuric urine has always appeared to me more distinctly frothy than any urine I know of. The reaction of the urine is acid or neutral: I have found both. The specific gravity is low (1010 to 1016), and there is a large amount of albumin in the urine. The albumin may be as much as half the volume of the urine tested. There is a quick deposition of the albumin, and the chamber-pot, if examined a quarter of an hour to half an hour afterwards, may show the albumin sticking to the bottom and sliding in the direction in which the pot is inclined to. This I have observed frequently in my own and other cases. Very soon the chamber-pot becomes stained of a yellow-red colour. I attribute this to hæmatin and bile pigments. The appearance of the urine, if more carefully examined, makes one suspect the presence of bile pigment. Delicate tests for pigment and fluorescence applied to it will confirm this. As to the hæmoglobin, one would expect it to be oxyhæmoglobin, and this, too, can be confirmed. Methæmoglobin has been found. There is no sugar in the urine in the uncomplicated case of blackwater. The microscopical examination of the urine will reveal the presence of blood corpuscles, usually more or less broken up, hæmatin crystals, some renal epithelium and débris (some of this might be crystallized bile pigment). In more severe cases there may be found "casts" from the kidney, but the ordinary case will not show this, indicating the absence of any extensive damage to the kidneys.

The patient is usually mentally anxious about himself, and frequently easily excited. In cases where there is hyperpyrexia there is delirium. The patient having lost, and losing, a large amount of the body fluid, is very thirsty. The heart beats, as a rule, faster, and the pulse is lowered in volume, and is easily compressible. There may be hæmic murmurs. The heart is easily excited, and the slightest movement in a severe case may accelerate the pulse-rate. Owing to the poor nourishment the heart receives, from the hæmoglobinæmia and anæmia, and from it having to pass this lessened blood fluid with less nourishing contents through the body at a quicker rate, the heart is very liable to shock. In some cases I have noticed epistaxis, which may be regarded favourably. Œdema of the feet may be present.

A very unfavourable sign is the supervention of ANURIA, which has to be watched. As a rule, in the early stages of the illness, the patient will urinate every half hour to one hour. Great attention should be paid to the fact that he has urinated, and all urine passed should be seen and examined as to the quantity passed and its colour. This attention to the quantity passed may give an indication if there was a tendency to anuria supervening. So long as the patient is drinking plenty of fluid the chances of anuria supervening are very greatly lessened.

#### CHAPTER III.

#### QUININE AND BLACKWATER.

IF quinine was the cause of blackwater fever then obviously if one gave a large dose of quinine blackwater should be the result, whether in a malarial or a nonmalarial case. I know many planters who have taken large doses1 (not at my suggestion)—even to 40 grains in a single dose—and have not had blackwater fever or any dreadful result. Again, we should see no case of blackwater fever where no quinine has been taken. But cases are on record where blackwater fever has occurred in patients who have never taken quinine. A few isolated cases where quinine, even in small quantities, have induced hæmoglobinuria may only show once again how every drug might find specially susceptible people to its action. In my opinion, however, in view of the theory expounded herein, these cases might be explained thereon, owing to the administration of quinine, at a time when suffering from malignant tertian malaria they had also congested livers. In such cases, I say, quinine will induce the attack, but this attack might have come on without the exhibition of quinine. All malignant tertian malarias, in my opinion, tend towards blackwater fever, i.e., hæmoglobinuria as a complication, and whether the hæmoglobinuria will come or not depends upon the degree of congestion of the liver at the time of the attack and its relief. It does not necessarily need to be a severe degree

<sup>&</sup>lt;sup>1</sup> By a large dose is meant over 10 grains at a dose.

of "fever" attack to bring about a hæmoglobinuria; it depends upon the degree to which the liver is congested. A mild attack of fever might, with a highly congested liver, give rise to hæmoglobinuria, and if the liver is speedily relieved the hæmoglobinuria will speedily disappear. I have seen several cases of severe malignant tertian malaria with high fever, congestion of liver, congestion and enlargement of spleen, bilious vomiting and some pigmentation of the skin with very dark red urine. These cases would not, from the colour of the urine, be put down as blackwater fever, and my category of blackwater fever cases, to hold to the usual diagnosis, would exclude them. But these cases are nothing less than mild blackwater fever-mild, so far as the urine condition is concerned. These cases present the difficulty of knowing where malignant tertian ends and blackwater fever begins. I believe they show us that all malignant tertians tend to blackwater—if the liver condition permits—and that all malignant tertians, if they were untreated, would either kill the patient by the successive attacks or end in blackwater. Recovery in such cases would depend upon the constitution of the individual.

The proof of the pudding lies in the eating thereof, and if quinine was the cause of blackwater fever one could not safely give large doses of it in the various forms of malaria. But one can give (not that I think large doses are necessary or essential to the cure of these fevers) large doses in simple tertian and quartan malarias without getting hæmoglobinuria. These fevers do not congest the liver so much or so quickly, nor is there the rapid or so great affection of the red blood corpuscles, as in malignant tertians. I have known men take 15 to 30 grains of quinine per day in the two former varieties, and no sign of any tendency to blackwater developed. In

malignant tertian, on the other hand, the exhibition of quinine in any large dose would depend upon the state of the liver, the amount already taken, and the regularity with which the drug had been taken previous to the attack. One could not give a large dose of quinine in a malignant tertian without running the risk of producing hæmoglobinuria if there was any degree of congestion of the liver, or if there had been an irregular taking of quinine, and a moderate dose had already been taken before the patient was first seen. It must be clearly understood that in these cases the quinine is NOT THE cause of the hæmoglobinuria, but that it acts as an excitant from the sudden destruction of a large number of red blood corpuscles at a time when the liver is unable to do its duty, to get rid of the hæmoglobin thrown into the circulating blood. If quinine was the cause of hæmoglobinuria then we would not be justified in giving the drug in the treatment of the condition. Not only do I not regard it as the cause, and advise that every case of blackwater fever requires immediate quinine, BUT that the quinine must be given very judiciously, and only after a purgative has been given to relieve the liver congestion (this is dealt with in treatment). A necessary corollary to these views would be that a person who cannot tolerate quinine should certainly not live in a district where malignant tertian malaria exists; but if I had not faith in cassia beareana as an alternative to quinine in such condition I would certainly subscribe to that view.

Quinine Poisoning v. Blackwater Fever.

Quinine may produce hæmoglobinuria in malarial or non-malarial patients, but in them you find:—

(1) A large dose of quinine has been taken, as a rule

(20 to 40 grains). (Where smaller doses have seemed to produce the attack it only proves, in my opinion, that bile pigments were still circulating in the blood, or the patient was specially susceptible to quinine.)

- (2) That "fever" is not necessarily present.
- (3) That liver congestion did not pre-exist as a necessity.
  - (4) Bile pigments are not passing out.
  - (5) The history helps.
- (6) A larger quantity of quinine is, on the average, excreted during hæmoglobinuria, and the excretion extends to a longer number of days.

#### CHAPTER IV.

#### POINTS IN FAVOUR OF MY THEORY.

- (1) BLACKWATER fever is only found in highly malarial districts.
- (2) Blackwater fever is usually found in the latter half of the year or at the commencement of a year—periods when malignant tertian malaria is rife.
- (3) Fever, rigors, enlarged spleen, and a malarial history are always found in the blackwater fever cases, showing its connection with malaria.
- (4) Intense jaundice and intense congestion of liver favour biliary theory as to origin of the hæmolysis.
- (5) Malignant tertian parasites can be found in the blood before the hæmoglobinuria. (I have found them.)
- (6) High percentage (20 and over) of large mononuclear leucocytes point to its malarial origin, and such high percentage of these is only likely to occur in a malaria of severe intensity.
- (7) The reasons why natives do not seem to suffer so much as Europeans is probably due to a partially acquired immunity from childhood, and possibly to non-recognition, for we know negroes are not exempt from it, nor Bengalis living in highly malarial districts. Europeans who are getting constant fever, thus rendering their livers congested, although they have been only a year or two in the district, may get the affection, but the mass of evidence (Plehn) would seem to be that the longer the

residence in a highly malarial district, the greater the chances of becoming affected, and such greater period of residence must have an injurious effect on the liver.

- (8) Why some malarial districts seem to be free of blackwater fever may be accounted for by the absence of the malignant tertian parasite there, or the absence of the "special malignancy" of this variety of parasite in that district. All malarial districts are not equally malarial, nor are all highly malarial districts equally highly malarial, or, in other words, all highly malarial districts need not contain very malignant parasites malignant to the same degree. The more regular taking of quinine in certain districts would also, to a small extent, help to explain this absence of the condition, as also of acquired immunity in persons there. Plehn has shown that those who take quinine regularly enjoy an immunity; this is what one would expect, and, it supports my theory.
- (9) The presence of bile pigments in the urine shows their presence in the blood, which is also shown by the skin pigmentation. In all cases bile in the urine (urobilinuria) need not be demonstrable to any great extent.
- (10) Kala-azar can be excluded, as one never sees hæmoglobinuria in a kala-azar case, nor do we see a blackwater fever case degenerating into the terrible picture of a kala-azar case. On the contrary, too, recovery from blackwater fever under proper treatment is most rapid, and a patient can be, in my opinion, as robust as ever, provided he does not live in a highly malarial district. This could not be in a kala-azar case, although there may be a so-called temporary recovery.
- (11) Focal necroses in liver are found post mortem in blackwater fever, pointing to the serious derangement of the liver leading to its inability to do the extra work called upon it, and the presence in the blood of bile

pigments—of varying composition, and possibly imperfectly elaborated. The pathological changes in the liver are greater than in the spleen.

- (12) Its prevalence in "livery" subjects.
- (13) The sudden taking of quinine after an irregular period of quinine-taking often leads to hæmoglobinuria. Such irregular taking gives rise to repeated attacks of fever, which leads to congestion of liver; then the sudden dose further depresses the liver action, leading to the hæmolysis and hæmoglobinuria.
- (14) Since Celli (p. 47) says the red blood corpuscle may be, in æstivo-autumnal fevers, destroyed by hæmolysis even without the parasite invading the corpuscle, it points to some combination such as my theory suggests, viz., that of the bile pigment imperfectly formed, or in combination with quinine, causing the explosion of hæmolysis. Without bile pigment in the blood I believe no blackwater occurs with or without quinine, and that quinine alone is not the cause is proved by cases occurring where no quinine has ever been taken, and also by the fact that quinine does not reproduce it when the bile pigments have disappeared from the blood in the treatment of blackwater.
- (15) Where repeated attacks of malignant tertian fever occur, rendering liver congested, these conditions of the urine appear very difficult to distinguish from blackwater fever.
- (16) Preliminary congestion of liver and prodromal symptoms (pain over gall-bladder, &c.) before hæmo-globinuria occurs.
- (17) The absence, or difficulty in finding, of malignant tertian parasites in the blood of a patient with blackwater fever is in accordance with the behaviour of this parasite, and is *negative* evidence in favour of the

relationship of blackwater to the malignant tertian parasite. The parasite, however, can be found before the hæmoglobinuria occurs.

- (18) The temperature chart in a marked case of any duration is related to that of a malignant tertian infection.
- (19) The greater excretion of quinine during blackwater fever is against the view that quinine causes blackwater fever by the action of some poisonous element separating from it.

# CHAPTER V.

### PREDISPOSING CONDITIONS.

Conditions under which blackwater fever may arise are:—

- (1) A sudden chill on the liver in a person affected by the malignant tertian parasite.
- (2) A chill to one about to have an attack of malignant tertian ague.

These (1) and (2) may be in persons who have

- (a) Not taken quinine at all.
- (b) Taken it irregularly, but have not taken a sudden dose to destroy the attack caused by chill.
- (c) Taken it irregularly, but took a sudden dose of quinine (moderate or large) to destroy the attack caused by chill.
- (3) Repeated or recurrent attacks of malignant tertian fever causing congestion of the liver.

IN ALL CASES when there is congestion of liver, bile pigments circulating in the blood in a malignant tertian attack or infection. Evidences of bile in the blood:—

- (1) Pigmentation of skin, sclerotics, sweat.
- (2) Presence in the urine as detected by fluorescence and other tests.
  - (3) Bilious vomiting.

### CHAPTER VI.

Some Points on the Action of the Malarial Parasites on Red Blood Corpuscles and their Relation to Quinine, with some Thoughts and Questions.

SIMPLE tertians and quartans are never pernicious and yield easily to quinine, whilst the æstivo-autumnal variety of the parasite is extremely pernicious, develops rapidly, and is more resistant to quinine, therefore less quinine as a prophylactic is required in the earlier half of the year when the former reign, and quinine should be taken more carefully, regularly, and in larger doses, immediately before and during the months of the latter parasites' reign. The detection of crescents make the diagnosis of æstivo-autumnal infection certain. Some recognize two varieties of the æstivo-autumnal parasite, one having a cycle of existence of twenty-four hours (true quotidian), and another a cycle of forty-eight hours (malignant tertian). It is most probable that the malignant tertian may have, according to its inherent severity, or according to the lowered resistance of the red cells, a shorter cycle of twenty-four hours. In other words, I believe malignant tertians may develop in from twenty-four to forty-eight hours, according to favourable or unfavourable environment. The main seat of infection in them is generally recognized to be the internal organs, especially the spleen and bone-marrow, and such forms as are found in the blood are regarded as

purely accidental. But the discovery of small parasites in the blood shows that in certain stages of the development the parasite may be found in the peripheral blood. Probably because the parasite is so small in its earlier stage the early detection in the peripheral blood is a matter of difficulty, and it is probable also that there is only one variety of the æstivo-autumnal parasite, but which, according to its severity, malignancy, or the resistance power of the patient's blood, varies in its cycle of development between twenty-four to fortyeight hours. The association of hæmoglobinuria with severe forms of fever is old. While malarial parasites in cold-blooded animals reduce the hæmoglobin very little, and in general do not destroy the red blood corpuscles, those of birds, and still more of man, nourish themselves at the expense of the hæmoglobin (converting it into melanin), and finally destroy the red blood corpuscles. Malaria of oxen in the Agro-Romano was common with hæmoglobinuria, high fever, jaundice, and death (Celli). In birds, malaria frequently causes hæmoglobinuria. A tick transmits the malarial parasites to bovines. It has been said that the red blood corpuscles may be destroyed by hæmolysis in æstivoautumnal infection before even the parasite has invaded the blood corpuscle, and we can have hæmoglobinuria, as we have, in the case of malaria of bovines and other mammifers. Hæmoglobinuria is only a complication, in my opinion, of malignant tertian malaria, in so far as it occurs in malignant tertian malaria when there is acute congestion of the liver. The reason why it should so occur may not be plain at present, but in my view, it is because when there is an excess of bile pigment (and probably one special form of bile pigment, e.g., biliverdin), that this in some way causes an explosion

of the corpuscles affected. This may be Nature's way of getting rid of the parasite in the corpuscle. That it has occurred in cases where no quinine was taken favours this view. It is possible also that the combination of quinine and bile pigment together form a substance producing hæmolysis. If blackwater fever be the result of malignant tertian, and if in malignant tertian the rule is that most of the parasites are in the spleen and only involution and young forms in the peripheral blood, is it possible that the severe infection of the blood, i.e., large number of infected corpuscles going to the spleen, the spleen enlarges and expels the imperfect forms from it with new-formed blood corpuscles? I think not, and regard the enlargement of the spleen only as a response to the demand for more new red corpuscles for the use of the patient.

It is possible, however, that blackwater fever may be related in some mysterious way to the flagellate bodies of the malignant tertian parasite; and though I put this out as a suggestion I am not inclined to believe this (till proved), since it would appear to me that we should have blackwater fever less prevalent if these forms are so rare, and its tendency to increase (?) (or discovery) in any district is rather against the idea, for why should these forms tend to become more frequent with malignant tertian infections now than keep to their previous relatively rare finding?

If areas of local necrosis in liver have any relation to producing attacks of hæmoglobinuria, then it is possible that it is one to the liberation into the bloodstream of a stage in the bile pigment which is particularly toxic to the corpuscle, and this would further support my view. It is not the result of a toxin of the malaria parasite, as extensive destruction of red corpuscles may occur without a febrile attack, e.g., poisoning by chlorate of potash, carbon monoxide, &c., which cause great destruction of blood corpuscles without a febrile attack. No toxin has been found. Lastly, in blackwater fever the temperature found is that of malignant tertian. The name of blackwater fever should be expunged and BILIOUS MALIGNANT TERTIAN AGUE substituted.

## CHAPTER VII.

THE LIVER FACTOR IN BLACKWATER FEVER.

In every malarial attack there is a hæmoglobinæmia, and this does not under ordinary circumstances pass through the kidneys, as the liver is quite able with simple tertian and quartan infections to take up the hæmoglobin from the blood plasma and convert it into bile pigments. According to the degree of destruction of red blood corpuscles there is a corresponding degree of anæmia and polycholia. But in blackwater fever, the parasite being so pernicious or malignant, there is either a very rapid and severe infection of many red blood corpuscles and, or, or combined with this, there is the elimination of a toxin, so powerful that there is a rapid destruction of the red blood corpuscles. As to the evidence in favour of the former suggestion we can imagine the parasite having a rapid life-history, analogous to the rapid spore formation theory of small-pox infection, and this would support the quotidian idea, but against this is the fact that blackwater fever cases do not show the quotidian type of fever we would expect, and also since quinine in some malignant tertians does not act so efficaciously as in the simpler varieties of malaria it is not likely quinine would act as efficaciously in a quotidian fever due to a severe type of the parasite as it does. Against the view of any special toxin being generated by the parasite causing the hæmolysis is the fact that blood taken from a blackwater fever case and injected into animals and men have not caused blackwater. The only evidence of a toxin we have, is the presence in the blood of bile

pigments which, either by themselves, from some cause such as imperfect elaboration from severe congestion of the liver, or in combination with quinine, cause the hæmolysis. I regard the condition of the liver as being all important in the production of blackwater fever. There are very many cases of æstivo-autumnal infection, and yet all such do not end in blackwater fever. But if the liver is congested in a slight degree either from recurrent attacks of fever or accidentally as from a drinking bout with a fresh infection, the next attack of fever will be marked with a high colouration of the urine; and the more congested the liver the higher or darker the colour, so that with some cases of æstivo-autumnal infection it is difficult to say how far the term blackwater fever would be applied to it. When, in such an infection as æstivo-autumnal fever, which specially demands that the liver above all organs should be especially capable of dealing with the rapid or large destruction of red blood corpuscles, there happens to be a highly congested liver, which is incapable of rising to the duty required of it, then the hæmoglobin becomes a foreign body in the plasma, and the kidneys are irritated to excrete it. We can easily understand how a patient, being infected with the malignant tertian variety of the parasite, who has not been taking his quinine regularly, and whose liver is congested from the attacks of the infection, makes matters worse by taking a sudden large dose of quinine, by the depressing action of such a dose on an already sluggish liver. In this way quinine can produce the hæmoglobinuric condition, in my opinion. We find many cases of blackwater fever related in their history to the sudden taking of a moderate or large dose after an irregular taking of the drug. Again, repeated attacks of malignant tertian fever will give rise to attacks difficult to differentiate from mild blackwater fever.

# CHAPTER VIII.

### TREATMENT OF BLACKWATER FEVER.

THE general lines of treatment are :-

- (1) Relieve the liver congestion.
- (2) Destroy such parasites as are present by judicious exhibition of quinine or cassia.
  - (3) Relieve distressing symptoms.
  - (4) Counteract shock.
- (1) The liver congestion, I find, is best and easiest relieved by EPSOM SALTS. My routine is always to give ½ oz. to I oz. of mag. sulph. in blackwater fever or any malignant tertian case. This mag. sulph. flushes out the stomach and duodenum of excess of bile and relieves the liver congestion. By doing this it also relieves the tendency to that distressing symptom—vomiting. In my own case the exhibition of I oz. of mag. sulph. so relieved the liver that I never once vomited. This is a tremendous gain to the patient. A hot fomentation to the stomach will lessen the tendency to rejection. If rejected you must repeat it, as it means everything to your patient to keep down a good dose of mag. sulph. in the early stage. If the vomiting is excessive you may be compelled to use \( \frac{1}{4} \) grain morphia. I never give calomel and certainly do not advise giving it, as it has a tendency to make your patient sick, or feel sick, and distress him; and also you are not sure of your patient having nephritis.

(2) To destroy the parasites. Quinine is the usual drug used. The parasites must be destroyed. If malignant tertian parasites have originally caused the condition of the liver, leading up to the hæmoglobinuria, are you going to allow a continuance of the parasites in the blood to repeat the condition? This is a question the physician must answer. There is only one answer, and that is, the parasites must be destroyed by some drug that will do this. If you resort to quinine, then you have to consider the amount of the drug already taken and the regularity with which it has been taken. The quinine is only to be given after the purgative chosen has been given. Information as to the amount taken, and the regularity of the taking, is in my experience very unreliable, but you have to go on what is told you, though you may alter your opinion on this from other factors. It will usually be found that quinine has been taken irregularly, and then a sudden large dose was taken. If the dose has been very large, one should not give any more, but simply watch the result of the drug, the condition of the patient, and the character of the urine, and act as one thinks best, and wait twenty-four hours to decide about quinine. Then the guides are the blood and the temperature. If the amount of quinine has been a moderate quantity and the temperature is high I certainly advise quinine. If the quinine has been taken regularly, and the amount taken for the attack was not over 15 grains, I advise the immediate injection of quinine after mag, sulph, has been given. If the amount of quinine taken was small in any case I would advise cassia beareana 3i. to 3ii. every hour or two. After four to six hours, if the temperature fell, one would be justified then in starting with quinine. One has to give quinine even at the risk of restarting hæmoglobinuria

if quinine is the only drug that will kill the parasite. A return of the hæmoglobinuria with quinine circulating in the blood could not be so dangerous to the patient as the risk to him of a recurrence of the hæmoglobinuria without quinine in the blood. It is not necessary that large doses of quinine should be administered, and I do not believe in giving quinine in any other way than by the intramuscular injection in blackwater. In the first place you do not wish by the giving of the quinine to upset his stomach or restart his vomiting. Secondly, you wish to be sure that the quinine gets there, and that quickly; and that only such quinine as you want need be put into the patient. This is best done by the intramuscular injection. I always use in such cases, and in severe malarias, the intramuscular injection of 3 grains of quinine bihydrochloride into the deltoid; it could be done in the buttocks and elsewhere, but I always do it into the deltoids. In no case have I ever had any trouble from it. There may be a little pain occasionally, but that usually passes off in a day or two. The needle and syringe are easily sterilized in boiling hot water in a teacup, and a teaspoon is also similarly sterilized in a few minutes. Your tablet of quinine is put into the teaspoon and 10 drops of hot water put on to it by your syringe or needle. The tablet is dissolved quickly—and in this it can be accelerated by the glass piston (of your glass hypodermic syringe) which has been in the boiling hot water—and having drawn it up in your syringe, all is ready in fifteen minutes. The patient's arm is sterilized either by a handkerchief kept soaking in another cup of boiling hot water or a dilute carbolic solution. If I have methylated spirits I sterilize the needle in a flame in addition. Whenever there is a tendency for the temperature to rise I believe in giving an intramuscular injection of quinine.

A severe case might require a repetition of the injection within twelve hours; a moderate or mild case could wait twenty-four to forty-eight hours before the injection is repeated, but there is nothing to be gained by delaying injections or repeating them too often.

The only other way of giving quinine that does not appear objectionable to me is the rectal use of quinine. Hypodermic injections of such are to be condemned, as they are both painful and the acid salt irritates the soft cellular tissue.

Besides quinine there is cassia beareana, which might be used intermittently along with quinine. I have found it highly useful, and have touched on this in another chapter.

(3) Distressing Symptoms.—Vomiting is often a most distressing symptom. Remember it is Nature's method of getting rid of a lot of excess of bile, and does good and draughts of cold water, even if rejected, do good by washing out the stomach. It is a mistake to interfere too early. I use hot fomentations to the stomach to allay it and give ice to suck. Both I have found most successful, and the cessation, even if temporary, gives rest to the patient. The latter also gives fluid to the system, which it is in sad need of.

Thirst.—The question of giving fluid to the system is very important. The patient by the hæmoglobinuria has lost a lot of fluid and collapse may follow owing to the heart being badly nourished and having little to contract upon. The patient may drink, ad lib., of water, soda water, barley water, milk and soda, egg flip, and may also suck ice. A little champagne is permissible and does good.

Of drinks, I have found egg flip, champagne, and ice invaluable. The fluids also have a third good effect, viz., they help to flush the kidneys. This is of great value,

since it will prevent chances of albuminous coagulation in the renal tubules and thereby prevent that serious complication—anuria, or suppression of the urine.

Shock.—To prevent this the patient should be given plenty of fluid and be kept absolutely recumbent. I cannot insist upon this point too much.

# Cassia Beareana in Blackwater.

There is one drug which requires mention in the treatment of blackwater fever besides quinine, and that is cassia beareana (the liquid extract). I am not in a position to say whether it has any specific action in this disease, nor do I think those who hold it has such an action are. What I do know is that, given in the doses recommended (mxxx. to mlx.), it is of no value. But I have used it in larger doses, 3i. to 3ii. in one, two, three, or four hours, and have found it a cardiac tonic, a diuretic, and a diaphoretic. These three actions must be useful in this condition. It certainly has a tendency to break the fever, and in cases of malignant tertian, bordering on blackwater fever, it has acted in its antiperiodic effect like quinine. If it does this (as it does) then it would point to having an effect like quinine in destroying the malarial parasite. I think that we want this drug to be taken up more, and its properties and actions more scientifically enquired into, for, as I say, I have observed the above effects when using doses larger than those ordered and usually tried. I have found it useful in malignant tertian malarias, and intend trying its effect this year on a larger scale in malarial fevers generally.

Removal of Patient.—I am strongly of the opinion that the patient should be taken out of his environment at the earliest possible moment coincident with safety. Besides acting as a fillip to the system, the change to a cooler climate retards the development of the parasite to a certain extent. If you get your patient early, remove him at once, having sufficient blankets, fluids for ingestion, &c., with you. One can always arrange this, and with sufficient covering and care there is no risk of a chill.

The Return to the District.—This, in my opinion, is a question of constitution of the patient and his ability to take quinine. If his constitution is good, and he can take his quinine and have mosquito wire netting to his verandah and bedroom, there is no reason why he should not return. If, on the other hand, he is weakly and can or cannot tolerate quinine, he should not for either reason return to the district. If his constitution is good, but tolerance of quinine is not as good as one would like, vet he could take cassia beareana or Warburg's tincture, and can live in a sanitary mosquito-proof house, I see no reason why he should not return to the district. For some reason or other I have always found that men who are teetotallers do not seem to stand malaria so well, and seem more liable to it than those who indulge in alcoholic drinks. It may be that the alcohol in the blood inhibits the development of the parasite.

### WHY IS BLACKWATER FEVER SO DREADED?

In the first place, so far as statistics go, and they vary very much (4 to 5 per cent.), it has a moderately high mortality. This mortality, in my opinion, is due for the most part to the improper recognition of the cause of the disease, and therefore in the variability of the lines of treatment adopted. Furthermore, since the majority of medical men have had little or no experience of the disease and its symptoms, unjustifiable conclusions

regarding the same have been adopted, and insufficient and wrong interpretations have been put on the symptoms. If a man does not recognize the great necessity for the recumbent posture, nor the great necessity for giving fluid to the already drained system, he may in other ways relieve his patient's symptoms, yet will surely lose his case. Again, if another refuses to give quinine when the temperature continues to rise, and hæmoglobinuria recurs, he will surely lose his case.

### PATHOLOGICAL LESIONS.

Kidney Lesion.—Because the kidneys secrete albumin in the urine many have come to the conclusion that there must be a nephritis. Albumin is frequently secreted normally (physiological albuminuria), and in blackwater fever you do not find, as a rule, renal tube casts indicative of a severe pathological lesion as nephritis. In cases where post mortems have been made no evidence of nephritis was found. No one denies, nowadays, the existence of physiological albuminuria. Blackwater fever is one of the instances where Nature calls upon the kidneys to act vicariously, so to speak, for the benefit of the system. The kidneys pass the hæmoglobin and albumin, and if no coagulation of the latter occurs in the kidneys they may recover themselves, in my opinion, to the normal state. If there is nothing abnormal in the urine six months after a repeated examination I would pass this point in favour of the candidate for life insurance.

Spleen.—In my own case I could watch the spleen enlarging from day to day. The enlargement of the spleen is, I would like to insist, a natural compensatory hypertrophy of the organ. The system is denuded of numbers of blood corpuscles. What more natural than

that the organ which has to replenish these quickly must, from the extra work thrown upon it, enlarge? When in cardiac affections the heart enlarges is it not compensatory hypertrophy? So, too, when one kidney is diseased the other enlarges on the call of extra work. The sudden and great enlargement of the spleen is also another reason for the great need of absolute recumbency of the patient. It must be remembered that the capsule of the kidney is stretched and that rest is required for the spleen in its extra work, as also to prevent rupture of the capsule. The enlarged spleen is tender to the touch, and even slight movement caused, in my own case, pain in the spleen, showing that rest to this organ is indicated.

### COMPLICATIONS.

Anuria is dangerous and has to be met with rapidity. Hot packs and hot drinks are indicated. Pay great attention to the quantity of urine passed each hour to get an indication whether anuria is likely to supervene. I have seen anuria in one case, and in another it threatened.

Hyperpyrexia.—In one of my cases delirium followed this. It is a very unfortunate occurrence, as it means your patient is likely to weaken himself by any struggling. Hot packs failed, and reduction by means of ice to the forehead, arms and legs was successfully accomplished. The temperature should be kept below 102°F. I have used a tepid bath in hyperpyrexia successfully, taking care of the reduction. Avoid phenacetin, antipyrin, &c.

Epistaxis I have seen in malignant tertian bordering on blackwater, but I regard it as favourable and not of any serious import.

Hæmorrhage from Bowels.—This is possible. Fæces are dark stained, either with bile or plus blood. I have seen

hæmorrhage from the bowels occur in a case of chronic malaria which had been operated upon by me for hæmorrhoids, and on examination by me and two other medical officers of the Royal Army Medical Corps, showed no trace of bleeding anywhere in the field operated upon. This was regarded by us as a case of melæna.

Shock must be treated in the usual way. Saline rectal injections and infusions will both be found useful, and hypodermic injections of strychnine and digitalin have to be given.

### Preventive Treatment.

This, for blackwater fever, I regard to be that of malignant tertian malaria. Those in malarial districts should in the first half of the year take quinine in *moderate* doses REGULARLY, say 10 grains every four or five days (various preventive quinine doses are given in the appendices). In the earlier half of the year I am of the opinion that this dose should suffice for simple tertians and quartans. From July the quinine should be taken oftener, 5 grains night and morning daily (or, at any rate, every other day at the least). In addition to this it is necessary to avoid chills, and to keep under mosquito-proof wire netting in the evening when not working and sleep under such, or under mosquito nets (20 meshes to the inch). The bowels should be kept regularly open. All servants should be carefully treated at the same time. They should be compelled to use mosquito nets. There should be an inspection of these from time to time. Antimalarial measures should be taken against the possible chances of breeding grounds for mosquitoes around bungalows. Guests with malaria should be given quinine and put to bed with mosquito nets.

All such measures combined should exterminate blackwater fever.

# Quinine Prophylaxis:

Koch's system: 1—1½ grammes on 10th and 11th or 8th and 9th days.

Celli's ,, 4 grains daily.

Italian ,, ½ gramme every day.

Plehn's ,, ½ gramme every 5 days.

Ziemann's ,, I gramme every 4 days.

Newell would advise during earlier months (January to June) 10 grains (5 grains morning and night) on every 4th day of a month and last day of month; and during July to December 5 grains night and morning daily. Bowels kept open.

(During July to December 1 liability to malignant tertian infection exists, and such infections do not react so easily to quinine as the benign forms of malaria, and hence the necessity of greater dosage of quinine during these months.)

MORTALITY.—There should be none. The disease is preventable. If taken early, judicious treatment should save all. Out of 16 cases (10 natives and 6 Europeans) all Europeans recovered. In the case of the natives they were either seen too late, had too little stamina, were unwilling to take fluid nourishments suggested, or had great fear, which accounted for their deaths. In 2 of 16 cases malignant tertian parasites were found before hæmoglobinuria occurred, and in one during hæmoglobinuria—but all cases were not examined for parasites.

<sup>&</sup>lt;sup>1</sup> These months refer specially to highly malarial districts in India.

## CHAPTER IX.

### THE CAUSE OF DEATH.

THE cause of death in blackwater fever is shock. In blackwater fever there is not only a large destruction of red blood corpuscles, so important to the individual cells of our various tissues, but there is also a concomitant loss of the fluid of the blood. In consequence, apart from the lessened nourishment of the tissues, the heart has very little fluid to contract on, and has to contract the more rapidly to hurry the lessened and poorer fluid more quickly through the body. These factors will soon play it out if means are not taken to overcome them. Therefore more fluid is desired, as evidenced by the great thirst, and *fluid ad lib*. should be allowed the patient for the three reasons stated.

To prevent death you want:-

- (1) To supply *fluid ad lib*. to give fluid to the system, to give fluid to the heart to contract upon, to dilute the bile pigments, to flush the kidneys, to carry out the newformed blood cells from the compensatorily enlarged spleen, and to carry such through the blood-vessels.
- (2) Rest—absolutely in the recumbent posture—to lessen irritation and extra work to the weakened heart.
- (3) To lessen force of heart within limits, if necessary, to permit it getting as much nourishment as possible. This is partly secured by rest, but I believe also by cassia beareana acting like digitalis.
- (4) To destroy the parasite (but not by too vigorous attempts) by the judicious exhibition of quinine, and undoubtedly preferably by the intramuscular method.

# CHAPTER X.

## CASSIA BEAREANA.

Cassia beareana is named after Dr. R. O'Sullivan Beare, who first used it in East Africa, where the native medicine-man (or Wa-ganga) claim for it a specific effect in blackwater fever. Dr. Sullivan Beare has recorded five cases in which no quinine had been taken two months before, and has stated (Lancet, February 1, 1902) that blackwater fever "undoubtedly attacks native Africans who have never taken a dose of that drug." I differ from this medical gentleman in considering the symptoms due to a toxin pure and simple, and have to state that search for a toxin has been carefully made by Celli and others, who have failed to find any. If a toxin was the cause of the hæmoglobinuria pure and simple, then blood from such a case should, when injected into mammifers or man, produce a like result. This has been done by some without effect. It is important to note that the natives of East Africa drink a decoction of the leaves of cassia beareana, and it would appear to me that this produces a better effect than the liquid extract. Twelve pieces of the root, each I in. long, are boiled in a gallon of water for an hour or so, and the decoction is given in a teacupful every two hours. In this way I think the patient gets a stronger dose of the root extracts than in the liquid extract, and since the liquid extract is ordered to be given in the small doses referred to (mxxx. to mlx.) it is not surprising that many have found the drug useless. I find that Dr. Beare in one case gave as much as I oz. of the liquid extract. I did not know this before I tried my doses, and I am sure that the liquid extract, if used in doses of 3i. to 3i. would give success. But surely it is time that its true dose was settled, as it gives good effects in some hands, as in mine, with larger doses than those on the bottle, and I believe a valuable remedy against blackwater fever (and malignant tertians) is being overlooked. Some firm of chemists might well make a fluid extract with a dose of 3i. to 3i. to be taken every two or three hours, according to the case (to be ordered by a medical man). A decoction means too big a dose at a time to be taken.

# CHAPTER XI.

#### CASES.

#### Case I.

THE chief facts in the author's own personal case were:—

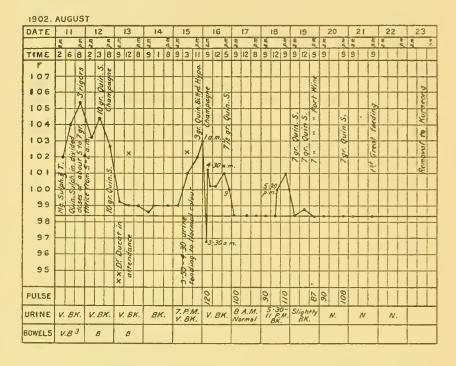
- (1) I was a malarial subject, and sixteen months in the Dooars.
- (2) There was a slight enlargement of the spleen for a few days before the attack, and the liver was congested.
- (3) I had not been taking quinine very regularly before the attack, and what quinine I took a few days before the attack was small in quantity.<sup>1</sup>
- (4) I experienced a chill on the two nights before the attack.<sup>2</sup>
- (5) The hæmoglobinuria began very soon after the attack of fever came on, and before a large quantity of quinine was taken. The initial fever began at 2 p.m.,

I returned to the Dooars from Kurseong on August 9—after having been there a week, where I left my wife. My wife was very ill in the Dooars for three weeks, and during this time I was constantly in attendance both day and night, and during this time neglected my quinine. The bungalow in which we lived was placed in the midst of jungle, and in this bungalow my predecessor also had blackwater fever. The doctor before my predecessor also had blackwater, but in another bungalow on the same estate, and also badly placed (though well placed for every chance of malaria). I believe his predecessor had blackwater in that same bungalow. These comprised all the European medical officers who had been appointed in that district. My successor had a slight attack of blackwater in the same bungalow as I lived in.

<sup>&</sup>lt;sup>2</sup> On the night of arrival (9th), in my district, after riding about 10 to 12 miles, I got wet by a shower of rain about a mile from my bungalow. On the following night (10th), on returning from a planter's bungalow, I experienced a strong wind, which I felt cold.

and quinine (5 to 7 grains) was taken at 5 p.m. (as I was run out of stock and had to await its arrival), and the hæmoglobinuria started about 7 p.m.

- (6) Vomiting was avoided by an early and large dose of mag. sulph. relieving congestion of liver.
  - (7) The fæces were very dark coloured.
  - (8) Rigors and prostration were intense, with high fever.



- (9) Temperature lowered and condition improved by quinine.
- (10) Initial yellow pigmentation of skin did not exist (probably because liver congestion relieved), but occurred on the second day, and recurred with the relapse.
- (11) Spleen was very greatly enlarged (to the umbilicus) and extremely tender.<sup>1</sup>

<sup>&</sup>lt;sup>1</sup> Spleen reduced rapidly on improvement, and could not be felt under the ribs a few months later. This shows compensatory hypertrophy.

- (12) There was intense pain over right kidney. There was no pain over the left. The right kidney had a mustard plaster applied to it which gave relief.
- (13) With the relapse of the hæmoglobinuria (August 15) there was tenderness over left lobe of liver coincident with skin pigmentation, and the tenderness was relieved by a mustard plaster.
- (14) There was frequent desire to pass urine and an abnormal amount was passed. The urine was hæmoglobinuric and evidently bile-stained, and large deposits of albumin in the chamber-pot.
- (15) The relapse with hæmoglobinuria occurred with a cessation of quinine and improved on taking quinine, and ceased the day after quinine was resumed.
- (16) I attribute my recovery to the initial mag. sulph., quinine, champagne, ice, and Brand's essence of chicken. My convalescense was rapid after removal to the Hills.
- (17) The temperature chart is instructive. The first recurrence of the temperature took place in the evening of August 15, and, if we allow for the amount of quinine taken on August 12, it points to a delayed tertian fever; and, again, taking August 16 as a day on which there was fever all day, there was a tertian rise of fever on the night of the 18th. On taking a more continuous course of quinine thereafter there was no further rise of temperature.

August 12, 1902. 1.40 p.m.—Brand's essence.

1.55 p.m.—Mustard plaster to kidneys.

2 p.m.—Temperature 103'1°.

2.30 p.m.—10 grains quinine.

3.15 p.m.—Temperature 104'1°.

4.30 p.m.—Temperature 103'1°.

5.15 p.m.—Brand's essence.

5.30 p.m.—Temperature 103°.

6 p.m.—Taken by Mr. Clifford to Huldibari T.E.

7.15 p.m.—Arrived at Huldibari.

8.30 p.m.—Temperature 102.8°.

8.45 p.m.—Brand's essence.

9.15 p.m.—10 grains quinine.

9.20 p.m.—Vomited.

13th. 12.15 a.m.—Brand's essence. Temperature 99.1°. Urine very black all day.

12 noon.—Dr. Ducat arrived. Temperature 99°. Urine very black all day.

14th. 9 a.m.—Temperature 98.6°. Brand's essence.

12 noon.—mv. solution of arsenic. Temperature 99°.

1.30 p.m.—Temperature 99°.

1.45 p.m.—Brand's essence. Urine black all day.

15th. 3 p.m.—Dr. Ducat left. Urine tending to normal.

3.30 p.m.—Temperature 101°. Soup.

4.30 p.m.—Temperature 104'1°. Urine bad colour.

5.30 p.m.—Brand's essence. Temperature 101.2°.

7 p.m.—Temperature 102°. Urine very black.

8.30 p.m.—Temperature 101°.

8.45 p.m.—Jelly.

11 p.m.—Temperature 102°. Soup.

16th. 1 a.m.—Temperature 103°. Urine very bad.

1.50 a.m.—Temperature 103.2°.

2 a.m.—Champagne. 3 grains quin. bihyd. hypodermically.

3.30 a.m.—Temperature 96.8°.

4.30 a.m.—Temperature 101.2°.

6.30 a.m.—Temperature 101°. Soup.

9.20 a.m.—Mustard plaster over stomach.

9.30 a.m.—Temperature 100°2°.

10 a.m.—Brand's essence.

1 p.m.—Temperature 100°.

1.45 p.m.—Temperature 100.8°. Jugged soup.

5.45 p.m.—Temperature 101°.

6 p.m.—7½ grains quin. sulph.

7 p.m.—Temperature 100.4°.

8 p.m.—Brand's essence.

9.30 p.m.—Temperature 100°.

10 p.m.—Soup.

17th. 4 a.m.—Soup.

5.30 a.m.—Champagne.

8 a.m.—Temperature 98·4°. Brand's essence. Urine normal colour.

10.40 a.m.—Brand's essence.

1.35 p.m.—Soup. Urine normal.

5 p.m.—Brand's essence.

7.30 p.m.—Champagne.

8.30 p.m.—Soup.

10 p.m.—Mixture. (Liq. arsen. hydrochlor. mvii., liq. strych. hydrochlor. mv., aq. 3ss.) Pulse 100.

11 p.m.—Urine normal.

18th. 8 a.m.—Urine normal.

12.35 p.m.—Brand's essence. Urine normal.

1.30 p.m.—Champagne. Urine normal.

4 p.m.—Brand's essence. Urine normal.

5.30 p.m.—Urine black. Temperature 100°.

6.15 p.m.—Soup.

8.30 p.m.—Brand's essence.

8.45 p.m.—Urine, no improvement.

9 p.m.—Temperature 101.4°.

9.20 p.m.—Mixture. Pulse 108.

9.30 p.m.—Cream pudding.

11 p.m.—Mixture. Urine nearly normal.

12 p.m.—Brand's essence.

19th. 1 a.m.—7 grains quin. sulph.

3.30 a.m.—Mixture. Brand's essence. Urine nearly normal.

9 a.m.—Temperature 98.8°; pulse 87. Brand's essence.

9.20 a.m.—Soup.

10 a.m.-7 grains quin. sulph

10.15 a.m.—Mixture.

тт a.m.—Port wine.

11.30 a.m.—Soup.

1.45 p.m.—Soup.

4 p.m.—Port wine.

4.30 p.m.—*Mixture*.

4.45 p.m.—Brand's essence.

5 p.m.—Port wine.

5.45 p.m.—Soup.

6.45 p.m.—7 grains quin. sulph.

8.30 p.m.—Mince, pudding, port wine.

20th. 2 a.m.—Urine normal. Brand's essence.

4 a.m.—Port wine, tonic mixture. Urine normal.

7.30 a.m.—Soup.

8.30 a.m.—Cornflour.

9 a.m.—Mixture.

ro a.m.—Egg and milk.

12 noon.—Soup, minced chicken, pudding, champagne.

3 p.m.—Mixture. Urine not quite normal (?). Port wine.

5.15 p.m.—Soup.

6.15 p.m.—Mixture.

7 p.m.—7 grains quin. sulph. Egg and milk.

8.30 p.m.—Pulse 108.

9 p.m.—Soup, pigeon, pudding, champagne.

21st. 3 a.m.—Champagne.

5 a.m.—Brand's essence.

8.15 a.m.—Soup. Urine normal.

9.15 a.m.—Cornflour.

10 a.m.—Egg and milk.

11 a.m.—Soup.

12 noon.—Soup, fowl, custard pudding, port wine.

# EXPLANATION OF CHART 2, p. 49.

B. = Black.

V.Bk. = Very black.

P.W. = Port wine.

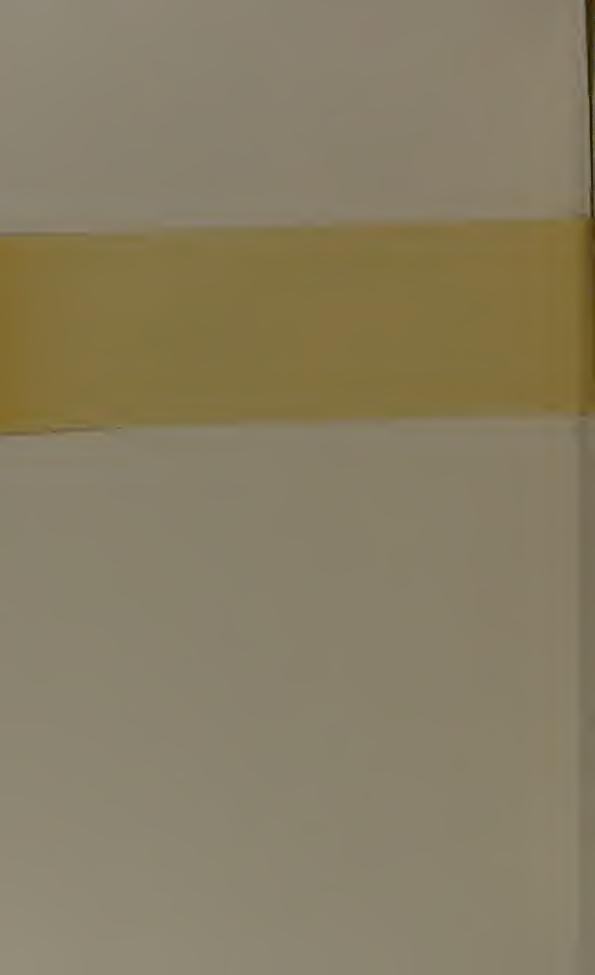
S.R. = Sherry red.

V.G. = Very good.

S.R.C. = Sherry red colour.

S.L.R. = Slight light red.

D.R. = Dark red.



CASES

3 p.m.—Port wine.

4.30 p.m.—Soup.

5.30 p.m.-Milk.

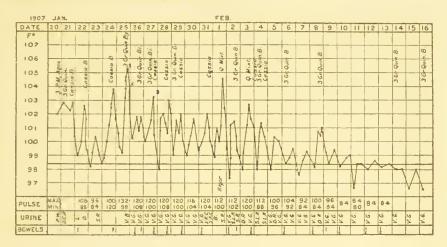
8 p.m.—Soup.

9 p.m.—Dinner—Soup, side dish and vegetables, pudding, second champagne.

Note.—For the noting of these details and for attention to me, I am deeply indebted to Mr. and Mrs. C. W. Clifford's great kindness.

#### Case 2.

A. R. M., assistant tea planter, aged 26. European, born in India, where he has always resided. Took up his billet in the Terai in February, 1906, before which he had been on a hill tea estate.



He was taken ill on Friday, January 18, 1907, with fever and feeling out of sorts. The night previous had ridden home about midnight from another bungalow. On Saturday, the 19th, took scarcely anything to eat and had fever all day. On Sunday was seen by me, when I found him with a temperature of 102° F., congestion of liver, and spleen slightly enlarged and tender. Had yellowish tinge of face and a great tendency to vomit.

On Saturday, the 19th, he took 10 grains quinine bisulph. ("tabloid") in the morning and 5 grains in the evening. On Sunday morning he had taken 5 grains of quinine. On this day I saw him at II a.m. and ordered him zvi. mag. sulph. and 12 grains quinine bihydrochloride by mouth, to be repeated in four hours. The mag. sulph. was taken, but the quinine bihydrochloride was not taken as he felt so bad. At 3 p.m. he had an ague fit, and passed portwine-coloured urine. He passed port-wine-coloured urine up to Sunday evening. I was wired for at 8.45 p.m., and arrived (after riding 18 miles through the dark night) at 4.15 a.m., when I found his temperature 102.6° F., urine dark cherry red colour and frothy. The bowels had been moved three times and the stools were of a muddy colour. I gave him an intramuscular injection of quinine bihydrochloride, 3 grains, into left deltoid. The temperature kept at 102° F. till Monday evening. (Took six specimens of blood from left lobule of ear and examined urine.)

21st.—Afternoon took soup; thereafter to eve had also egg flips and champagne.

5.5 p.m.—Gave 3i. cassia beareana.

6 p.m.—Temperature 102.2°. Soup.

7 p.m.—Temperature 102.6°. mxxx. cassia beareana.

8 p.m.—Temperature 101.6°. Brand's essence.

9 p.m.—Temperature 100'4°. mxxx. cassia beareana.

22nd. 9 a.m.—Temperature 99°. Milk.

12.30 p.m.—Temperature 100°. Vomited after stool. Urine lighter colour. Champagne (a little). Allowed to suck ice from 3 p.m.

3.30 p.m.—Temperature 102.6°; pulse 120. 5i. cassia beareana.

4.15 p.m.—Temperature 102°. Soup.

5.30 p.m.—Temperature 101.6°. 5i. cassia beareana.

6.30 p.m.—Temperature 101'4°; pulse 108. Soup.

7.45 p.m.—Temperature 100°; pulse 96. Little soup.

8.15 p.m.—Temperature 99°; pulse 88.

10.30 p.m.—Temperature 99°; pulse 88.

12 midnight.—Temperature 99.4°. Urine dark-coloured.

23rd. 2 a.m.—Temperature 98·2°; pulse 84. A little champagne.

3.45 a.m.—Temperature 99'4°; pulse 84.

4.30 a.m.—A little soup.

5 a.m.—Temperature 99'4°; pulse 96.

8.30 a.m.—Temperature 99'2°; pulse 96.

9 a.m.—Soup.

10.30 a.m.—Temperature 99'2°; pulse 88. Milk.

12 noon.—Soup.

r p.m.—Pudding.

2 p.m.—Temperature 100'4°; pulse 100.

2.30 p.m.—Passed urine.

2.45 p.m.—Temperature 99.8°; pulse 96.

3.30 to 4.40 p.m.—Changed bedrooms for airing.

4.45 p.m.—Temperature 99.4°; pulse 96. Little milk.

5.40 p.m.—Half cup soup.

7 p.m.—Little milk. Slept one hour.

8.30 p.m.—Temperature 99°; pulse 96. Half cup soup. 12 midnight.—Temperature 98·4°; pulse 108 (?). Cup of milk.

24th. 12.30 a.m.—Urine sherry-red colour and smell of natural urine.

3 a.m.—Temperature 98.8°; pulse 92. Soup.

4.30 a.m.—Champagne.

6.15 a.m.—Temperature 98.8°; pulse 88.

8 a.m.—Champagne.

8.45 a.m.—Temperature 99°; pulse 108.

9 a.m.—Tonic. Complains of headache.

9.15 a.m.—Milk.

10.30 a.m.—Temperature 100°; pulse 100. Eggs and toast.

11.15 a.m.—Temperature 99.4°.

12 noon.—Temperature 100'2°; pulse 96. Tonic. Slept.

1 p.m.—Temperature 101.2°; pulse 100. Soup.

1.15 p.m.—Temperature 100°; pulse 108. 5 grains phenalgin.

2 p.m.—Soup. Temperature 101'2°; pulse 100.

3 p.m.—Temperature 101'2°; pulse 100. Blancmange and custard.

4 p.m.—Temperature 102°; pulse 104. Cornflour and milk. Slept.

5.30 p.m.—Temperature 102.4°; pulse 108. 3i. cassia beareana.

6 p.m.—Enema.

6.30 p.m.—Temperature 102.6°; pulse 108. Good motion.

7 p.m.—Soup.

8 p.m.—Temperature 103.8°; pulse 110.

8.15 p.m.—Temperature 103°; pulse 120.

9.15 p.m.—Temperature 103°.

10.15 p.m.—Temperature 101.6°; pulse 108.

25th. 12.30 a.m.—Temperature 101.4°; pulse 112.

2.45 a.m.—Temperature 100.6°; pulse 104. Soup. Slept.

5 a.m.—Temperature 99'6°; pulse 96.

8.30 a.m.—Temperature 99'4°; pulse 94. Tea.

9.15 a.m.—Temperature 100°; pulse 100.

9.20 a.m.—Tonic.

10 a.m.—Temperature 99'2°; pulse 98. Arrowroot.

11 a.m.—Brandy.

11.15 a.m.—Temperature 100°; pulse 104. Soup.

12.15 p.m.—Cornflour.

12.30 p.m.—Temperature 99.6°.

2 p.m.—Tonic.

2.10 p.m.—Temperature 103°2°; pulse 120. Liebig's soup.

3 p.m.—Urine hæmoglobinuric.

3.10 p.m.—Temperature 103.8°; pulse 132. Champagne.

3.45 p.m.—Intramuscular injection; 3 grains quin. bihyd. Soup.

4.30 p.m.—Temperature 103.6°; pulse 132.

5.30 p.m.—Temperature 104'2°; pulse 128. Wandering.

6 p.m.—Temperature 104'4°; pulse 132. Champagne (iced). 3i. cassia beareana.

6.30 p.m.—Temperature 104.6°; pulse 128 (very weak).

7 p.m.—Temperature 105'1°; pulse 108. Iced applications.

7.30 p.m.—Temperature 103°; pulse 128. Iced champagne.

8 p.m.—Temperature 104'2°; pulse 124. Diaphoretic 8.30 p.m.—Temperature 105°; pulse 128. Four blood films taken.

8.45 p.m.—Temperature 104'2°; pulse 132. Urinated.

9 p.m.—Temperature 105°; pulse 132. Wandering. Injected intramuscularly 3 grains quin. bihyd. Diaphoretic (9.10).

9.30 p.m.—Temperature 104°; pulse 132. Delirious.

10 p.m.—Temperature 103'4°; pulse 128.

10.15 p.m.—Temperature 103.6°; pulse 132.

10.30 p.m.—Temperature 104°; pulse 132 (weak). Hot pack. Dr. H. arrived.

11 p.m.—Temperature 104°; pulse 128. Dr. H. left.

11.45 p.m.—Temperature 103.4°; pulse 132. Ice to head, arms, and legs.

26th. 12.15 a.m.—Temperature 103°; pulse 132.

12.35 a.m.—Temperature 102°; pulse 120. Slept.

2.45 a.m.—Temperature 102·2°; pulse 118. Soup. Urinated. Slept.

6.30 a.m. — Temperature 100.2°; pulse 102. Tea. Urine very good colour.

8.15 a.m.—Temperature 100.2°; pulse 108.

9.30 a.m.—Temperature 100°2°; pulse 106.

10.15 a.m.—Cornflour.

11.15 a.m.—100.4°; pulse 106. Liebig's soup. Urinated (good colour).

11.45 a.m.—Little brandy.

12 noon.—Soup.

12.30 p.m.—Temperature 100'4°; pulse 120. Enema given, which acted. 3i. cassia beareana.

1 p.m.—One cup of milk.

2 p.m.—Temperature 101.8°; pulse 118.

3 p.m.—Temperature 101.2°; pulse 120.

3.15 p.m.—3 grains quin. bihyd.

4 p.m.—Liebig's soup. Bowels moved. Urine very good colour.

4.15 p.m.—Temperature 101.4°; pulse 118. Little fruit.

5 p.m.—Temperature 100.4°. Raw egg (of which patient is very fond).

6 p.m.—Temperature 100.8°; pulse 108.

7.45 p.m.—Temperature 101.6°; pulse 112.

10 p.m.—Temperature 101.6°; pulse 108. Milk. Bowels moved. Urine good colour.

10.10 p.m.—Sleeping draught. Slept 10.30 p.m. to 2.30 a.m.

27th. 2.35 a.m.—Temperature 100°; pulse 108.

3.30 a.m.—Milk. Urinated; good colour.

5.30 a.m.—Temperature 100'4°; pulse 108.

7.30 a.m.—Temperature 100'4°; pulse 108.

8 a.m.—Cornflour.

8.30 a.m.—Raw egg.

9.30 a.m.—Temperature 100°; pulse 108.

10.30 a.m.—Temperature 100.2°; pulse 108.

10.45 a.m.—Milk.

11.45 a.m.—3i. hæmatogen (Hommel's).

12.30 p.m.—Temperature 101.6°; pulse 114. A little brandy. Urinated.

I p.m.—Temperature 101'4°; pulse 116. Two blood films taken. 3 grains quin. bihyd.

1.15 p.m.—Blancmange and pear syrup.

2.30 p.m.—Temperature 101.2°; pulse 100.

3 p.m.—Liebig's soup; minced chicken; jelly; blanc-mange.

3.30 p.m.—Temperature 101°; pulse 112. Slept till 5 p.m.

5.15 p.m.—Temperature 103.2°; pulse 120. A little tea. Mother arrived and saw patient.

6 p.m.—Temperature 102'2°; pulse 124. 3i. cassia beareana. Enema.

7.15 p.m.—102<sup>2</sup>°; pulse 124. Milk. Slept.

8.50 p.m.—Temperature 100'4°; pulse 108.

11.30 p.m.—Temperature 100'2°; pulse 108. Sleeping draught. Slept.

28th. 1.30 a.m.—Milk. Urinated; good colour.

2 a.m.—Temperature 98°; pulse 108. Mag. sulph. Urinated; good colour.

6.30 a.m.—Tea.

7 a.m.—Temperature 99.6°; pulse 108.

8.30 a.m.—Milk.

9.15 a.m.—Temperature 100'2°; pulse 108. Urinated; good colour.

9.30 a.m.—Milk.

9.45 a.m.—Temperature 100.8°; pulse 108. 3i. cassia beareana.

10.30 a.m.—Tea.

11.30 a.m.—Temperature 101.6°; pulse 116. Milk.

11.45 a.m.—Raw egg. Urinated; good colour.

12.15 p.m.—Temperature 102°; pulse 120. Milk.

12.45 p.m.—3i. hæmatogen.

1.15 p.m.—Soup, jelly.

1.30 p.m.—Milk.

2 p.m.—Temperature 101.8°; pulse 112. Enema.

3 p.m.—Milk.

4 p.m.—Temperature 101'4°; pulse 116. Milk. Urinated; good colour.

5.15 p.m.—Temperature 100.6°; pulse 120.

6 p.m.—Tea. Slept.

7 p.m.—Temperature 101°; pulse 116. Urinated; good colour.

8.45 p.m.—Milk.

9.5 p.m.—Temperature 103°; pulse 120. 3i. cassia beareana.

9.50 p.m.—Temperature 102°; pulse 120. Changed position in bed.

10.5 p.m.—Temperature 102°; pulse 118. Sleeping draught. Slept.

29th. 2 a.m.—Temperature 99°; pulse 100. Milk. Urinated; good colour. Slept.

5.30 a.m.—Temperature 100.8°; pulse 100.

6 a.m.—Milk. Urinated.

7 a.m.—Tea.

8 a.m.—Temperature 101.4°; pulse 116. Milk.

9.15 a.m.—Temperature 101.6°; pulse 120. Milk.

9.30 a.m.—3 grains quin. bihyd.

10 a.m.—Tonic.

10.15 a.m.—Milk; jelly. Urinated.

10.45 a.m.—Temperature 101°; pulse 116. Raw egg.

11 a.m.—Milk.

11.15 a.m.—Temperature 100.6°; pulse 110.

11.30 a.m.—Milk.

12.15 p.m.—Hæmatogen. Slept till 1.15 p.m.

1.15 p.m.—Temperature 101.2°; pulse 116. Milk. Slept till 2 p.m.

2.15 p.m.—Temperature 101.6°; pulse 118. Milk. Slept till 3 p.m.

3 p.m.—Temperature 102°; pulse 118. Milk. Slept till 4 p.m.

4 p.m.—Tea.

4.30 p.m.—Temperature 101.6°; pulse 116. 3i. cassia beareana. Slept till 6 a.m.

6.15 p.m.—Milk. Urinated.

6.45 p.m.—Enema with good effect. Urinated. Perspiring.

9.45 p.m.—Tonic.

11 p.m.—Temperature 100°; pulse 100.

30th. 5.30 a.m.—Temperature 99°; pulse 100. Slept all night. Milk. Urinated. Complained of sore throat.

7.30 a.m.—Temperature 99.6°; pulse 112. Tea.

9.15 a.m.—Temperature 99.8°; pulse 104. Milk. Urinated.

9.45 a.m.—Milk.

10 a.m.—3i. cassia beareana.

10.45 a.m.—3 grains quin. bihyd. injected intramus-cularly.

11 a.m.—Tonic.

11.15 a.m.—Temperature 100'4°; pulse 108. Raw egg. 11.45 a.m.—Milk.

12 noon.—Urinated.

ı p.m.—Temperature 100.8°; pulse 108. 3i. hæmatogen.

1.30 p.m.—Milk.

2 p.m.—Little milk.

2.45 p.m.—Milk.

3 p.m.—Temperature 100·4°; pulse 110. 3i. cassia beareana.

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3.30 p.m.—Milk.
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3.45 p.m.—Albumen water.

4.30 p.m.—Temperature 100.8°; pulse 116. Urinated. Perspiring.

5 p.m.—Temperature 101°; pulse 110. Liebig's soup.

6 p.m.—Little milk.

7 p.m.—Temperature 101.6°; pulse 120. Milk.

8.15 p.m.—Temperature 100.8°; pulse 110. Tonic.

12 midnight.—Temperature 99.2°; pulse 108.

31st. 3.45 a.m.—Temperature 99'2°; pulse 108. Milk. Urinated. Complains of sore throat.

7 a.m.—Temperature 99.6°; pulse 104. Tea.

7.45 a.m.—3i. cassia beareana.

8 a.m.—Enema with good effect. Urinated.

9.15 a.m.—Temperature 99.8°; pulse 104. Milk.

9.45 a.m.—Cocoa.

10.30 a.m.—Intramuscular injection, 3 grains quin. bihyd.

10.45 a.m.—Milk.

11 a.m.—Temperature 99.8°; pulse 110. Tonic.

11.30 a.m.—Milk.

12 noon.—Temperature 100.6°; pulse 110.

12.15 p.m.—Little milk.

1 p.m.—Temperature 101.6°; pulse 112. 3i. hæmatogen. Milk.

2.15 p.m.—Soup. Urinated; red colour.

2.35. p.m.—Milk.

2.45 p.m.—Temperature 102°; pulse 120.

3 p.m.—3i. cassia beareana.

3.10 p.m.—Milk.

3.30 p.m.—Milk.

4.15 p.m.—A little arrowroot.

4.30 p.m.—Temperature 101°; pulse 120.

5.15 p.m.—Mixture.

6.45 p.m.—Temperature 101'2°; pulse 116. Soup. Urinated.

8 p.m.—Temperature 100°; pulse 108. Throat feels better. Slept soundly all night.

February 1st. 2 a.m.—Temperature 98.8°; pulse 104. Milk. Urinated; slightly red.

6 a.m.—Temperature 99.4°; pulse 104.

8 a.m.—Temperature 100°; pulse 108. Mixture.

8.15 a.m.—Cocoa. Slept to 9 a.m.

9 a.m.—Temperature 100.8°; pulse 110. 3i. cassia beareana.

9.30 a.m.—Milk. Urine rather dark.

10 a.m.—Raw egg.

11 a.m.—Injection of quinine.

11.30 a.m.—Temperature 101°; pulse 108. Arrowroot (little).

12 noon.—Temperature 100°. Soup. Cachet of quin. hydrobrom. 1 grain.

1 p.m.—Temperature 100.6°; pulse 112. 3i. hæmatogen.

1.45 p.m.—Milk. Slept on and off during whole fore-noon.

2 p.m.—Mixture.

3 p.m.—Temperature 100'4°; pulse 108. 3i. cassia beareana.

4 p.m.—Little cornflour. Urinated.

4.45 p.m.—Coffee.

5 p.m.—Temperature 101'2°; pulse 100. Mixture.

5.20 p.m.—Coffee.

6 p.m.—Milk.

6.30 p.m.—Temperature 101'2°; pulse 108.

7.30 p.m.—Had a RIGOR. Urinated.

8.45 p.m.—Temperature 104.6°. Mixture (quinine, &c.). Urinated.

10.20 p.m.—Temperature 102.4°.

10.45 p.m.—A little cocoa.

2nd. 5 a.m.—Temperature 97.4°; pulse 96. A little milk.

5.45 a.m.—Cocoa. Urinated; good colour.

6.30 a.m.—Mixture. Milk.

7 a.m.—Temperature 98.8°; pulse 108. Enema with good effect. (Nurse added here, "Nearly got another rigor," which evidently meant patient felt "chilly" this morning with his sudden drop in temperature, and he may have been uncovered for some time before 5 a.m.)

8 a.m.—zii. brandy.

8.45 a.m.—Milk.

9 a.m.—Temperature 101.2°; pulse 116. 3i. cassia beareana.

9.15 a.m.—Milk.

9.30 a.m.—Mixture.

10 a.m.—Throat painted. Milk.

10.30 a.m.—Temperature 100.8°; pulse 112. Meat juice.

11 a.m.—Orange juice. Bowels opened.

11.30 a.m.—Milk.

12 noon.—3i. hæmatogen.

12.30 p.m.—Temperature 101.4°; pulse 116. 5i. mixture. Orange juice.

I p.m.—3ii. brandy. *Urine slightly red*. Patient was lifted to make mattress, and he complained of feeling faint.

2 p.m.—Milk.

2.30 p.m.—Temperature 100.8°; pulse 128. 5i. cassia beareana.

2.45 p.m.—Soup.

4 p.m.—Temperature 101°; pulse 116.

4.5 p.m.—Mixture.

4.30 p.m.—Slept 4.30 to 6 p.m.

6 p.m.—Temperature 100'4°; pulse 108. Urine slightly dark.

8 p.m.—Temperature 99'4°; pulse 102. 5i. cassia beareana.

9.15 p.m.—Milk. Urinated; good colour. Perspired a good deal.

3rd. 2.45 a.m.—Temperature 98°; pulse 100. Had a good night.

7.30 a.m.—Cocoa.

8.30 a.m.—3i. cassia beareana. Throat painted.

9.25 a.m.-Milk.

9.45 a.m.—Injection of quinine by Dr. H.

10 a.m.—Coffee.

10.25 a.m.—Temperature 99.2°; pulse 100. Milk.

11.15 a.m.—Milk.

11.30 a.m.—Orange juice.

12 noon.—Little coffee. Complained of feeling shivery; hot-water bottles applied, and extra covering.

12.30 p.m.—Temperature 101.2°. 3ii. brandy 3i. cassia beareana.

I p.m.—Milk. Mixture. Urinated; dark red colour.

1.45 p.m.—Soup.

2 p.m.—Temperature 102.6°; pulse 116.

2.15 p.m.—Milk.

2.30 p.m.—Milk.

3.15 p.m.—Temperature 102'2°; pulse 116. Albumen water.

3.30 p.m.—Milk. (I arrived. I was away for two days.)

3.45 p.m.—Meat juice.

4 p.m.—Milk. Mixture.

4.45 p.m.—3i. cassia beareana.

5.30 p.m.—Temperature 101.6°; pulse 116. Milk (little).

6 p.m.—Milk. Urinated; good colour.

6.30 p.m.—Temperature 101.8°; pulse 120.

7 p.m.—zii. brandy. Enema with good effect.

7.15 p.m.—Milk.

7.30 p.m.—Milk. Mixture.

8.15 p.m.—Milk.

9 p.m.—Milk. 3i. cassia beareana.

9.20 p.m.—Milk.

10 p.m.—Temperature 101°; pulse 110.

4th. 4.30 a.m.—Milk. Urine slightly red. Complains of pain at site of injection where Dr. H. injected quinine.

6.30 a.m.—Temperature 98·2°; pulse 88. Little tea.

8 a.m.—Temperature 98°; pulse 94.

8.30 a.m.—3i. cassia beareana.

8.45 a.m.—Milk.

9.30 a.m.—Cocoa. Urinated.

10 a.m.—Temperature 100°; pulse 108. Milk.

11 a.m.—Chocolate.

11.3 a.m.—Temperature 100.6°. Little milk. Quinine injection.

12.15 p.m.—3i. hæmatogen.

ı p.m.—Soup.

1.15 p.m.—Temperature 101.2°; pulse 112. 5i. cassia beareana.

2 p.m.—Milk. Urine red colour.

2.15 p.m.—A little milk. Tonic.

3.15 p.m.—Temperature 101'4°; pulse 112. Valentine's meat juice.

4.15 p.m.—Raw egg and milk. 3ii. brandy. Biscuit.

6.30 p.m.—Temperature 100'4°; pulse 108. 3i. hæmatogen. Pain in stomach. Enema with good effect. Urine good.

7.15 p.m.—3ii. brandy.

9 p.m.—Tonic.

5th. 5 a.m.—Temperature 98°; pulse 96. 3i. cassia beareana. Urinated good colour.

7.30 a.m.—Chocolate.

8.30 a.m.—Tonic.

8.45 a.m.—Milk.

9.30 a.m.—Valentine's meat juice.

10 a.m.—Temperature 98·2°; pulse 96. Milk. Urine good colour.

10.30 a.m.—Coffee.

11 a.m.—Soup.

12 noon.—3i. hæmatogen.

12.15 p.m.—A little milk.

1 p.m.—Temperature 100.4°; pulse 108. Egg flip.

1.15 p.m.—3i. cassia beareana.

2 p.m.—Milk. Urine dark red colour.

2.15 p.m.—Tonic.

2.45 p.m.—Milk.

3 p.m.—Temperature 100'2°; pulse 108.

3.30 p.m.—3i. hæmatogen.

3.45 p.m.—A very little "pish pash."

5 p.m.—Temperature 100'2°; pulse 100. Tonic.

6th. 2 a.m.—Milk. Urinated; good colour.

6 a.m.—Enema with good effect.

8 a.m.—3ii. brandy. Urinated; good colour.

8.30 a.m.—zi. cassia beareana.

8.45 a.m.—Milk.

9 a.m.—Temperature 98.4°; pulse 104.

9.30 a.m.—Tonic.

9.45 a.m.—Cocoa.

11 a.m.—Milk.

11.45 a.m.—Raw egg.

12 noon.—Temperature 98.8°; pulse 94.

12.20 p.m.—3 grains quin. bihyd. intramuscular injection

I p.m.—A little pudding. 3i. hæmatogen.

1.45 p.m.—A little bread and milk. Tonic.

2 p.m.—Temperature 99'2°; pulse 92.

2.10 p.m.—Little soup. Urine good colour.

3.30 p.m.—Cocoa.

4 p.m.—An egg.

4.30 p.m.—zi. hæmatogen.

5.15 p.m.—Valentine's meat juice.

6 p.m.—Temperature 99'4°; pulse 94.

6.30 p.m.—Dhal and bread.

7 p.m.—Tonic.

7th. 7 a.m.—Tea.

8.30 a.m.—Temperature 97.6°; pulse 84. Cocoa. Urine good colour.

9 a.m.—Tonic.

10 a.m.—Egg and bread and coffee.

11 a.m.—Soup and bread.

11.30 a.m.—Temperature 98.6°; pulse 84. 3i. hæmatogen.

11.45 a.m.—Milk; 3i. Valentine's meat juice.

12.10 p.m.—Soup.

1 p.m.—Temperature 98.6°; pulse 92. A little stew and gravy. Cocoa.

2.45 p.m.—Milk.

4 p.m.—Tea.

6.45 p.m.—Temperature 99'2°; pulse 94. Valentine's toast and gravy. Tonic.

7.30 p.m.—3i. hæmatogen.

8th. 6.30 a.m.—Temperature 98'4°; pulse 84. Tea.

8 a.m.—Tea.

8.30 p.m.—Tonic.

8.45 p.m.—Enema with good effect. Urine good colour.

9.30 a.m.—Temperature 98.2°; pulse 84. Milk and rice. Cocoa.

11.30 a.m.—Egg, bread, and cocoa.

12 noon.—Temperature 98.4°; pulse 88. 3i. hæmatogen.

1.30 p.m.—A little cocoa.

1.45 p.m.—Valentine's meat juice.

3.15 p.m.—Temperature 100.8°; pulse 100. Soup.

3.30 p.m.—Tonic.

3.45 p.m.—Quin. bihyd. injection. Cocoa.

4 p.m.—Urine dark red.

4.45 p.m.—Tea.

5 p.m.—Temperature 100.6°; pulse 100. 3i. hæmatogen.

6 p.m.—Temperature 101°. Cocoa.

9th. 6 a.m.—Temperature 99'2°; pulse 92. Tea. Urine good colour.

7.30 a.m.—Tonic.

9 a.m.—Temperature 98'4°; pulse 84. Milk and rice. Urine good. Bowels opened.

10.30 a.m.—Egg, bread, and cocoa.

11.30 a.m.—Temperature 98'4°; pulse 88. 3i. hæmatogen.

12.20 p.m.—Soup.

I p.m.—Milk. Tonic.

2.30 p.m.—A very little "pish pash."

2.45 p.m.—Cocoa.

3.30 p.m.—Soup. Urine good colour.

4 p.m.—Temperature 99'4°; pulse 96.

5 p.m.—Dhal; tea and two slices of bread.

7 p.m.—Curry and rice (a fancy); cocoa.

10th. 2.30 a.m.—Milk. Urine good colour.

8 a.m.—Enema with effect. Urine good colour.

9 a.m.—Milk and rice; slice of bread and jam and cup of tea.

9.30 a.m.—Temperature 98.2°; pulse 84.

9.45 a.m.—Tonic.

ro a.m.—Taken outside the house for the first time.

10.45 a.m.—Cocoa. zi. hæmatogen.

11.15 a.m.—Two eggs and bread.

11.30 a.m.—Brought in. 3iii. brandy.

12.30 p.m.—Temperature 98.4°; pulse 88. Curry and rice. Stewed prunes and custard.

2 p.m.—Temperature 98.8°; pulse 96. Mashed potatoes and soup. Tonic.

3 p.m.—Cocoa.

4 p.m.—Tea; bread and jam.

6 p.m.—Temperature 99°; pulse 88. Three cutlets and pudding.

11th. 7 a.m.—Temperature 97.6°; pulse 80. Tea.

9 a.m.—Milk, rice, and cocoa. Urinated.

9.45 a.m.—Tonic.

10 a.m.—Cocoa.

11.30 a.m.—Curry and rice.

12 noon.—Temperature 98'4°; pulse 80. zi. hæmatogen.

1.20 p.m.—Cocoa.

3 p.m.—Temperature 98.4°; pulse 84. Pudding.

4 p.m.—Tonic.

5 p.m.—Tea.

8 p.m.—Stew, two mutton chops and little potato.

12th. 7 a.m.—3i. castor oil. Urinated.

7.30 a.m.—Temperature 98°. Tea.

8.15 a.m.—Cocoa.

9.30 a.m.—Cocoa.

10.30 a.m.—Enema with effect. Urinated.

11.30 a.m.—Milk, rice, and cocoa.

12 a.m.—Cocoa.

1 p.m.—Tonic.

3 p.m.—Temperature 98.6°; pulse 84. 3i. hæmatogen.

13th. 7 a.m.—Tea.

7.30 a.m.—Enema with effect. Urinated.

8.30 a.m.—Rice, milk, egg, bread, cocoa.

10.45 a.m.—Temperature 98.2°; pulse 84. 3i.hæmatogen.

11.45 a.m.—Soup.

12 noon.—Sandwiches and cocoa.

2 p.m.—Curry and rice; pudding.

4 p.m.—Tea and sandwiches.

6.30 p.m.—Mutton stew; chocolate pudding. Had a good night.

14th. 7 a.m.—Tea.

9 a.m.—Rice; milk.

10 a.m.—Temperature 98°; pulse 84. 3 grains quin. bihyd. intramuscularly.

10.30 a.m.—Two and a half boiled eggs. Taken out into sun and kept out till 4 p.m. Hæmatogen.

4.20 p.m.—Temperature 98°; pulse 76. Soup, curry, rice, rice pudding. Urinated.

5 p.m.—Made an excellent tea.

7 p.m.—Mutton stew, and bread and potatoes.

15th.—Up 11 a.m. to 9 p.m.

8.30 a.m.—Rice, milk, cocoa.

9 a.m.—Temperature 97.6°; pulse 88. Ate meals well.

10 a.m.—Two eggs, bread, butter, cocoa.

11 a.m.—Hæmatogen, and at 9 p.m.

12 noon.—Sandwich, cocoa.

ı p.m.—5iii. castor oil.

2 p.m.—Curry, rice, bread pudding.

4 p.m.—Sandwich, tea.

16th. 11 a.m.—Temperature 97.6°; pulse 96. Hæmatogen and quin. bihyd.<sup>1</sup>

Where colour of urine is not mentioned it is understood to be of good normal colour.

N.B. — That with this patient 3i. cassia beareana produced diaphoresis in one to one and a half hours.

The throat condition complained of was really a very transitory congestion. The quinine mixture prescribed is as follows (January 29, 1907):—

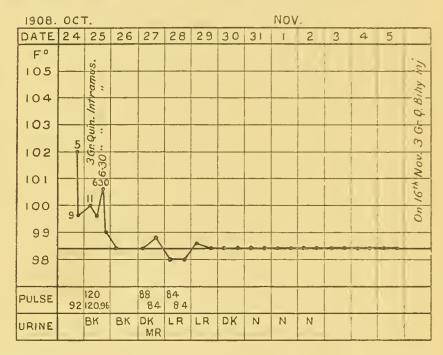
Ŗ	Quin. sulph			 	gr. xii.
	Ac. nitro. mur. dil.			 	5i.
	Liq. arsenici hyd.			 	mxl.
	Liq. strych. hyd.			 	ηxii.
	Tr. strophanthi			 	5i.
	Tr. zingiberis			 	Бііі.
	Syr. aurantii			 	5iii.
	Aq. menth. pip.			 ad.	ξvi.
	T	welve	doses.		

Sig., take one-twelfth part for a dose thrice daily.

<sup>&</sup>lt;sup>1</sup> Where quinine bihydrochloride is mentioned, it is to be understood that it is by intramuscular injection into deltoid, and if not so stated, it is of 3 grains quin. bihyd. (B. W. and Co.'s "tabloids").

## Case 3.

C. C. M., robust European, aged 30, born in India. Went home three years ago; came out in 1901, was on tea estate in South Sylhet for three years, where for the first six months he had slight fever. Came to the Terai, November, 1907, and joined the Tea Estate in the Terai, on which he was taken ill, February, 1908. Previous to that he came from the Dooars, where he had been three years.



When in the Dooars he had occasional malaria, but not severe. When in the Dooars he used to take quinine more or less regularly, but in irregular quantities, 5 grains daily or so and then 10 to 15 grains when not feeling up to the mark. Since being in the Terai he has probably taken less quinine. He took "chouthea" powders for about the first six months in the Terai, during which time he took no quinine. Thereafter to date of illness he took quinine irregularly, 5 to 10 grains on and off;

sometimes 20 grains a day. In connection with this attack, which is his first severe attack of fever, he felt out of sorts and feverish on Thursday, October 22. He had taken 20 grains of quinine that day (10 grains in the morning, 5 grains at noon, and 5 grains in the evening). He was prescribed, by me, a mixture containing 5 grains of quinine to the dose (combined with strych. hyd. and liq. arsenici hydrochlor.). Next day (Friday) he began the mixture and took three doses of it, and on Saturday (October 24) took it twice. He was "off his feed" for the last few days (22nd to 24th). He did not take his temperature during these days. The bowels said to be opened once daily. Got a shiver (ague) on Saturday, October 24, at 5 p.m., and began to vomit. He was given mag. sulph., 3ss. by his manager, who, curious to note, had the same name and was treated by me for blackwater (Case 2), and who remembered I strongly insisted on a preliminary dose of mag. sulph. in these cases. Thereafter also he got several doses of cassia beareana (the exact quantities are doubtful). His temperature had been that evening, before my arrival, 102° F. A Dr. Hindmarsh, who happened to be staying at a bungalow nearer than mine, was sent for pending my arrival. He had never seen a case of blackwater fever before. He prescribed the following mixture:

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      B. Ext. ergotæ liq.
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ix marks; sig., one mark in as much water every three hours.

This mixture was not taken. When I arrived at 11 p.m., the patient was alone and his temperature 99.6° and pulse 92. There was no specimen of his urine, and he sat up

OCTOBER, 1908. DAILY REPORT (CASE 3).

Date and Time	Tem- perature	Pulse	Bowels	Urine	Medicines	Remarks
24th. 5 p.m	102°	_	I	Black	zss. mag.	Ague; bilious
					sulph.; cassia	vomiting.
					beareana	
					between	
					5.30 and 8.30 (3	
					doses, I	
9 ,,	99.6°	92	I	_	believe)	Milk and soda.
9 ,,		9-	•			Hot fomentations.
25th. 9.30 a.m.	1000	120	_	Black	_	Ague and con- stant bilious
						vomiting during
						night
10 ,,	_		_	,,	_	Vomiting. Mus- tard plaster.
II ,,	—	—		—	3 gr. quin.	<u> </u>
					bihyd., intramus-	
					cularly	
11.30 ,,	_	_		_	_	Blood films taken. Lime juice en-
						joyed.
2 p.m.		_	_	Black	_	Fog Ain
3 ,, 6 ,,	99·6°			_	_	Egg flip. Vomited.
6.30 ,,	100.6 <sub>o</sub>	120	_	_	<b>—</b> .	D . 11
6.50 ,,	_	_	_	_	3 gr. quin. bihyd.,	Retching.
					intramus-	
0.20				_	cularly —	Vomited bilious
9.30 ,,						matter.
10 ,,	99°	96	_		_	½ gr. morphia.
10.15 ,,	_	90		Black		
26th. 6 a.m.	98·4°	-	_	Dark; lighter	_	Had good night's
				in colour than yester-		sleep. Milk and yolk of egg.
				day		
7.30 ,, 9 ,,			<u> </u>			Egg flip. Chicken soup.
9.15 a.m. to	Occur	ied in	iourne	to Kurseong.		r
3.15 p.m.	Secup	icu in		to ixurscong.		

OCTOBER, 1908. DAILY REPORT-continued.

Da	te and Time	Tem- perature	Pulse	Bowels	Urine	Medicines	Remarks
27th.	IO a.m. I2 noon	98·4°	88		Dark Muddy red	AA7-380	Egg flip. Chicken soup.
	6 p.m.	98·8°	84		During day passed small quantities of muddy red urine	_	Had good night's sleep.
28th.	9.45 a.m.	98°	84	_			
	6 p.m.	98°	84	1	10 oz. light brick red	A dose of mixture <sup>1</sup>	Spleen ½ in. less. Slept well during night.
29th.	IO a.m.	98.2°	84	I	Light red passed seve-	Mixture <sup>1</sup> twice	
30th		98·4°			ral times during day Dark red but clearer, i.e., not so "mud- dy" as yes-	to-day —	_
31st	***	98·4°	-	_	terday Urine nor- mal colour		<del>-</del>
Nove	mber I	98·4°	_	-	Urine nor-	AAPullia	_
2nd	•••	98·4°	-	-	Urine nor-	_	Up for an hour in afternoon.
3rd 4th		98·4° 98·4°	=	_		_	Had a short walk. Went to a concert.

<sup>&</sup>lt;sup>1</sup> Mixture contained quinine. Put on hæmatogen. Later, before return, to Terai had intramuscular injection of quinine. Is now taking quinine systematically.

and felt fairly well. Not knowing what drugs he actually had, and doubting then the case being blackwater, I stayed with him one hour. I gave him milk and soda, and applied a hot fomentation to the stomach. There being no accommodation there for me for the night, I rode off, after leaving instructions, to the manager's house. An hour later, patient said, he had an attack of ague, and constant vomiting during the night and early morning of the 25th.

On the 25th, 9.30 a.m., temperature 100°, pulse 120 (after vomiting); sclerotic and conjunctiva yellow, skin

deeply yellow, spleen enlarged and tender, liver congested. Mag. sulph. acted once in the night and at 10 a.m., 25th.

Urine of 24th, evening, acid, sp. gr. 1016. Dark claret colour. On heating, albumin present. No albuminous deposit in chamber-pot. On standing, the albumin obtained from treating the urine in test-tube was nearly half the volume of urine tested.

Urine of 25th, morning, 10 oz. in quantity, which is about the amount found in normal urine; sp. gr. 1016, and reaction acid. Hæmoglobinuric.

Quin. bihyd., 3 grains, was injected into right and left deltoid at 11 a.m. and 3 p.m. The vomiting on the 25th was severe in the evening, so to ease him I injected  $\frac{1}{4}$  grain morphia into pit of stomach at 10 p.m.

On the 26th, though the urine was decidedly dark, the patient was fairly well in other respects, and so he was carried up to Kurseong (9.15 a.m. to 3.15 p.m.).

On the 27th, morning, the urine was still dark, but the slightest degree lighter. Drs. Christophers and Bentley (on the Dooars Blackwater Fever Commission) telegraphed for by me, arrived at Kurseong, I p.m. and took patient's blood to examine for "complement." In the evening the urine was of a muddy red colour. Blood films showed increase of large lymphocytes, but no parasite.

On the 28th urine was a light brick-red colour, and the spleen was  $\frac{1}{2}$  in. less. Slept well.

The chief facts in this case were:—

- (1) Patient was a malarial subject, with recent history of fever favouring malignant tertian infection.
- (2) Had taken quinine irregularly for some time before the attack (admitted afterwards).
- (3) When attack was developing had a fair quantity of quinine.
- (4) Liver was congested during development and at time of attack.

- (5) Yellow tinge of skin developed second day of attack.
- (6) Vomiting of bilious matter present from onset and during the second day of the attack.
- (7) Had high fever before and during the attack, which was ushered in by a rigor.
- (8) Urine passed was hæmoglobinuric and contained bile pigment.
- (9) Though there was a large quantity of albumin, there was not that large quantity giving rise to deposition and adherence of albumin to the chamber-pot.

Note.—This case shows that the hæmoglobinuria succeeded in a malarial patient who had taken a fair quantity of quinine, after neglecting quinine-taking, and that his liver at the time was congested. The large quantity of quinine was sufficient to destroy the parasites and produce a rapid crisis and speedy recovery.

## Case 4.

Hem Chunder Dotto, aged 13. This boy, whose photograph is given as a frontispiece to illustrate the severe degree of emaciation to which kala-azar cases go, and which you do not see blackwater fever cases degenerating into, was first seen by me on May 5, 1905, in Calcutta. He was said to have been ill seven months (I have little doubt he was ill longer). His weight, naked, was 2 st. 9½ lb., and his height 4 ft. 3 in. In general appearance he was pale, with sunken cheeks and eyes; clavicles, acromion processes, scapulæ, condyles of humeri, ribs, all very marked (only covered with thin skin), showing great degree of emaciation. The thighs, buttocks, and legs had a little more tissue on them. The liver was contracted, being 2 in. in the right nipple line. Spleen: When lying down, the upper border of spleen

crosses over the upper border of seventh rib. From the costal margin (upper) of seventh rib downwards it is 3 in. Greatest breadth of spleen was 31 in. in the left nipple line. The greatest length was 7 in., and lowest point was 2½ in. from the umbilicus. On standing, the spleen falls down, the upper border coming to the lower border of the seventh rib, and the breadth in nipple line became 3 in. The greatest length became parallel to a line continued from the upper border of iliac crest. The bowels were usually loose—twice daily; motions yellowish, but sometimes whitish. Pupils dilated. Conjunctivæ extremely pale. Sclerotic absolutely white, with not the

1905.	MAY	,										
DATE	9	10	11	12	13	14	15	16	17	18	19	20
F°												
102											8	8
											/	
101											IA	10
100			A			A		7-1	-		A.	
1			$\Lambda$			$\Lambda$						
99												
98				0	7	V						
		1		\								
97					¥							
PULSE	128											

slightest tinge of yellow. The pulse was so small at wrist that it could not be counted. Heart-sounds by stethoscope 128 (4.30 a.m., May 9), and temperature 96.6° F. Ordered:

(1) B	Ferri et ammon.	cit.		 	gr. lxiv.
	Liq. arsenicalis		***	 •••	5i.
	Glycerini			 	₹i.
	Aq			 ad.	ξiν.
		Sig.,	3i. t.i.d.		
(2) B					gr. iii.

Sig., one at bedtime. (3) Maltine and cod liver oil, 5ii., twice daily.

Diet .- Good milk and rice.

On May 17 he weighed 2 st. 9 lb.

On May 20 he weighed 2 st. 10 lb. I ordered quin. sulph., 3 grains, night and morning, giving him twenty-four powders, also ung. hydrarg. iodid. rub. \(\frac{3}{2}\)i., of which a small piece was ordered to be rubbed every night into spleen at different spots. The salol was stopped. After the 20th I saw no more of the boy, who used to be very keen on paying his visits. I presume he died.



On the day I first saw this lad, May 5, 1905, I took some blood, with his permission, from the spleen, under very strict aseptic precautions. On May 7, 1905, I examined the specimens taken by ½th oil immersion lens; unstained specimen with good natural light. The following note was made at the time, and a diagram made of what was observed:—

Note.—Pyriform bodies, size of two or three red blood corpuscles, with evidently a nucleus at the broader part (the base) and a nucleolus at one side. Two of these bodies show a darker part at the base, and one shows the nucleolus at one side (on the convex curved side), and nearer the base than the apex. One of these bodies shows a distinct filiform appendage to the base; this body is evidently a more highly developed stage of the other bodies, being of larger size, though retaining the same shape, and shows more distinctly a nuclear condition at the base with the filiform appendage; no nucleolus could be made out. In the field where these bodies were found were four masses of pigment, well away from them, and there was no evidence of leucocytosis, there being only one leucocyte in the whole field. Several (nine) very small dark bodies, which do not appear to be pigment, appear in the field, and would seem to be degenerate corpuscles, one showing a corpuscular nature.

As this is a dried specimen, and taken direct from the spleen, it is evident these bodies occurred in the spleen during life, and very probably have a causal connection with the symptoms of the patient from whom they were taken. These bodies are not the Leishman-Donovan bodies, as they do not agree with the description of them. They are evidently of the nature of trypanosomes. This being so, then, the conclusion would seem to be that the development of a certain trypanosome in the spleen is the cause of those cases of which the main symptoms are enlargement of the spleen, progressive emaciation, anæmia, decrease of leucocytes, a peculiar earthy colour, and with looseness of the bowels; liver not necessarily enlarged. In this case, from which the specimen was taken, the liver was smaller than usual.

Case 5.

# Case of a Bengal Babu (Office Babu on Tea Estate in Dooars).

The patient was taken ill on May 22, 1901, with "fever," with remissions. I was called in on May 24 (I believe he was ill before the 22nd). He vomited a little on the 23rd, but this was said not to be bilious. Bowels had not been

1901.	MAY		
DATE	24	25	26
F°	Gr.		
106	00		
105	5		
104	-/	1	10:30
103	10	29	6 Noon
102	8	1/	Wo
101		5	Î
100		R	\$
99			
98		4	30.A.M.
PULSE	120	96 144 124 120 130	120 130
BWLS	- 1	2 5	1

moved for two days. Temperature on morning of 24th was 101.6° F. He had had 10 grains of quinine at 7 and 9 a.m. At noon on 24th he had bilious vomiting. Urine on 23rd was high coloured, but at noon on 24th was very dark coloured, and at 5 p.m. could be regarded as black. I saw the patient again at 6.30 p.m., when the urine was very high coloured, not "smoky," but obviously hæmoglobinuric. It coagulated almost en masse on

application of heat. Specific gravity 1015. Pulse at this time was very weak and fluttering, and temperature 105° F. I gave one pint enema of soap and water and castor oil, and antiseptically injected hypodermically 6 grains quin. bihyd. At 8 p.m. the temperature fell to 102° F., and the pulse was better at 120. At 8.15 p.m. he had a motion, chiefly of enema and small hard black masses of fæces. The tongue had a white fur in centre; the pupils were moderately contracted. There was no pain complained of anywhere, but on pressure the left kidney was slightly tender, and also liver. No yellowness of conjunctivæ. Ordered 10 grains of quinine every four hours, pulse and temperature to be noted, champagne at 10 p.m., milk and soda during night, and hot fomentations over kidney region. (The Doctor Babu who was with him was left in charge, and noted the details given in tabulated form.)

May 25.—Bilious vomiting at noon. Bowels twice opened and black. Pupils moderately dilated, and conjunctive yellow. Respiration hurried. Pain over liver and spleen. Urine obviously hæmoglobinuric.

Ordered (1) Liq. arsenicalis miss. and tinct. iodi. mii. when tendency to vomit, and before taking quinine.

- (2) Liq. strych. hyd., digitalis, camphor, spr. chlorof. in water thrice daily, but not immediately after milk.
- (3) One pint of milk in one bottle of soda water, and 3iv. brandy to be taken as occasional drink.
- (4) Calomel 3 grains, quinine sulph. 5 grains, one powder only after a dose of (1).
  - (5) Ten grains of quinine every four hours.

At 7 p.m. temperature was 102° F., pulse 144. Bowels had opened four times with stools of normal colour. Urine same (hæmoglobinuric). Heart was weak, and so ordered the strychnine-digitalis mixture every three

#### TABULAR DETAILS OF CASE 5.

Date and	rature	Pulse		M	EDICINE	USED	Appearance of S	STOPLS AND US	Progress Report		
Hours	Temperature	Pu	No. 1 mixture			No. 5 quinine	No. 5 quinine Stools		Urine	Diet	Remarks
May 24th.	deg.F.					1		i I			
7 a.m.	101.6					Quinine, 10 gr.				•••	_
9 ,,	1					Quinine, 10 gr.	•••	T	p.,	***	_
12 noon						***		Bilious	Dark		_
5 p.m. 6.30 ,,			•••			6 au hamadaum	Enome simon		Black Dark	•••	_
8	105	120				6 gr. hypoderm.	Enema given Enema acted,				
۰ ,,	102	120					black masses				
9 ,,	102'4							1			
10 ,,	103			100				1			J —
11.20 ,,	104'4	ICO									-
25th.											
12.20 a.m.	104'4	130									_
2.20 ,,	102.3	110						]			
5.30 ,,	100.8	100									_
7.30 ,,	100.8	90 (?)				•••	•••				_
9.20 ,,	100.6	80 (?)	***						•••		_
10.10 ,,	100'4	100		•••		***	•••				_
12.15 p.m.	4	130	***			Used to gr					
2.30 ,,	102.6	125	Used		Used	Used to gr	Yellow-2	Tendency	High colour	No. 3	
2.30 ,, 4.50 ,,	102.6	120	U Sett	Used			One	Lindelley	angii colour	11	
5.35 "	102.6	130	Used	12	Used	Used to gr	Change little-1	Tendency	Reddish colour		_
8.30 ,,	102.0	120	33								_
8.35 ,,						Quinine, to gr.					_
9.23 ,,	102.5			Used			Change little-1	Tendency	Reddish colour	No. 3	
10.30 ,,	102.2	130	Used				Stool passes—1	21	,,	**	Respiration increases; breathing dif- ficult.
10.35 ,,				***		Quinine, 10 gr.	11 11 2			N	Duta i to to
11.35 ,,	100.6	130					,, ,, I			No. 3	Pulse intermit-
11.50 1				Used				<b>1</b>		,,	—
26th.											
12.3 a.m.	102'0	130								,,	-
12.50 ,,	101,0	130		Used							_
I 31										No. 3	
1.20 ,,	100.5	120				•••				***	
2.30 ,,		100	Used	***		0.1.1	Stool passes—1			•••	
2.35 ,,	99.2	110		Used		Quinine, to gr.			Quantity less	No. 3	
	98'4	120							,	-	
6 ,,	102.8	130		33				Vomit	,,	)1 )1	
6,30 ,,			Used			Quinine, 10 gr.					i —
10.30 ,,	103.4	130	,,	-0		***					_
10.35 ,,						Quinine, 10 gr.					_
12 noon	103.0	120		Used						•••	Hypodermic in- jection, 10 gr. digitalin.
12.25 p.m.							1.1				Ditto, 100 gr.



hours; milk and brandy every hour, and the quinine every two hours till 10 p.m., and then every four hours.

May 26.—At 3 a.m. the patient's urine began to get less, and his temperature at 4.30 a.m. fell to normal. At 6 a.m. it was 102.8° F., at 10 a.m. 103.4° F., and at noon 103° F. He vomited at six a.m. He was in a very weak condition, and at noon pulse got much weaker. Sudden cardiac failure occurred at 12.30, following on the anuria, and at 12.40 patient died, in spite of fomentations, hypodermics of strychnine, and digitalin.

[Note.—Observations during day of 24th, 25th, and 26th are mine; night records of the Doctor Babu in charge.]

Remarks.—Chief facts in this case:—

- (1) That this was my first case of blackwater.
- (2) That I believe quinine had not been taken regularly.
- (3) He was said to have had 10 grains at 7 and 9 a.m. on the day I first saw him (at 5 p.m., 24th).
- (4) He was a robust man, and I did not see him early. He was obstinate and had caste prejudices against taking various nourishments.
- (5) That there was congestion of liver, enlarged spleen, high fever and hæmoglobinuria.
- (6) That the exhibition of quinine reduced the temperature from 105° F. on the 24th to 100'2° F. on the 25th, and again from 102'6° F. on 26th to normal on morning of 26th.
- (7) That the *rapid* subsequent rise of temperature, considering anuria had set in, must be attributed to uræmic poisoning.
- (8) The initial constipation, the physique of the patient, his refusal of nourishments, and the setting in of anuria were all against this patient's chances of recovery.

BRIEF NOTE OF CASES OF MALIGNANT TERTIAN MALARIA.

(1) Case of L. R. Had fever, on November 7, 1908, with some vomiting; previously having fever every third day.

On 8th, had fever with severe vomiting.

On 9th, on my arrival (2.30 p.m.), temperature 100° F. Had had very little nourishment. Bowels were opened on

previous Saturday and before that on the Thursday.

Examination revealed spleen enlarged and hard, two fingers' breadth below ribs. Liver congested. Tongue coated with a thick white fur all over. Sclerotic posteriorly with yellow tinge. No marked tinge of yellow of skin; face flushed. Urine of a very dark red colour.

At 4.30 p.m. on same day gave 3 grains quin. bihyd. intramuscularly into left deltoid, also  $\frac{1}{2}$  oz. of mag. sulph., of which 3i. was returned.

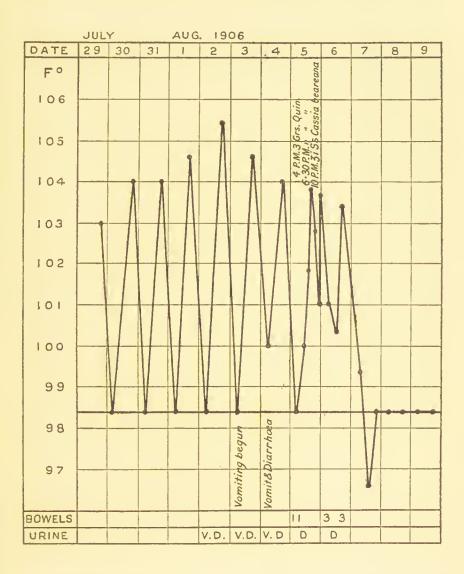
At 4.40 p.m. temperature was 104° F.

Taken to hills; put on quinine mixture as having slight

objection to injections. Made uninterrupted recovery.

(2) Case of H. W. G. Fever began about July 17, but first high temperature on eve of July 29, when he had a temperature of 103° F. Said to have taken some quinine on and off. Bilious vomiting began on morning of August 3, and on August 4 had, besides vomiting, diarrhœa, and after mid-day a temperature more or less constant at 104° F. I first saw him on August 5, at 11.30 a.m., when his temperature was normal, urine very dark, stools white in colour, and he had eleven stools that day up to my arrival. Liver congested, colour of skin yellowish. At 4 p.m. I injected 3 grains of quin. bihyd. and at 4.40 p.m. his temperature was 100° F. At 6.30 another intramuscular injection of 3 grains of quin. bihyd. was given, and at 7.15 p.m. his temperature was 101.8° F., and at 8 p.m. 103.8° F. He was sponged with vinegar and water, and at 8.40 his temperature was 102.8° F., and at 9 p.m. 101° F. At 9.25 his temperature was 101.6° F., and he was able to take and retain a cup of Liebig. At 10 p.m. he was perspiring, but his temperature was 103.6° F. He was at that time given 5iss. of cassia beareana, and at 10.30 was perspiring profusely. At 11 p.m. his temperature was 102'4° F., and he was given a sleeping

draught. At 1 a.m. (August 6) his temperature was 102° F. and he was given 5i. cassia beareana. At 8.30 a.m. his temperature was 101° F. and he was given 5i. cassia beareana. At 9.20 a.m. his temperature registered 99.4° F. At 10.30 a.m.



his temperature was 100° F., and he received intramuscularly 3 grains quin. bihyd. and was driven out to a garden near the hills, where he arrived at 12.45 p.m. At 2.30 p.m. his temperature was 101.4° F., when he received mxl. of cassia

beareana. At 6 p.m. his temperature rose to 102.4° F., when he was given 6 grains of quin. bihyd. At 8 p.m. the temperature was 103.4° F., and he vomited, and his temperature was the same at 9.30 p.m., when he retained some beef tea. He was given at 11 a.m. 3iss. cassia beareana, and at 12 noon his temperature was 101° F., and at 4 a.m. 100° F. At 1 a.m. (August 7) it was 102° F., but at 9.30 a.m. it was 99.4° F. At 10.30 it was 98.8° F., at 1.45 p.m. 96.6° F., and at 6 p.m. 98.4° F. After that he made an uninterrupted recovery.

Malignant tertian parasites were found, and the case is a good example of double malignant tertian infection and shows the value of quinine. It also showed marked diaphoresis by cassia beareana and the tolerance of this drug by the stomach

when quinine would not be tolerated.

(3) In another case of a European, although a large dose of quinine was given, the temperature remained at 105°, and it being inadvisable to give further doses of quinine, a good dose of cassia beareana was used with diaphoresis and fall of temperature resulting. In this case there was the usual history of fever every other day, and on the day before, as well as on day, I saw the patient there was bilious vomiting. The urine was highly coloured and would probably be called light port wine. Yellow pigmentation of the skin existed. Cassia beareana was continued for some days, and a rapid recovery resulted.

I could quote other similar cases, and cases might be multiplied, if closely looked for, of these severe malignant tertians bordering on blackwater. In my opinion all these cases would have terminated in marked hæmoglobinuria but for the previous taking of quinine, however irregularly. The amount of quinine taken was not sufficient to completely destroy the parasites. In each of these cases either pills or "tabloids" were taken. I do not believe absolutely sure results can be got from pills and "tabloids" of quinine, as often either they are not fresh or not dissolved. I strongly advocate the use of quinine in powder or solution, or periodic intramuscular injection of quinine.

A planter in the Dooars had an attack of blackwater fever (this he told me ensued on top of 40 grains of quinine), and about two years after had another attack which did not last long. He was sent to Darjeeling to recuperate. I saw him at Kurseong Station on his return after a week or ten days in Darjeeling, during which he took no quinine. I warned him he was returning too early, although he was anxious to return to work. Within a fortnight he was down with a severe attack of blackwater fever and left India, after recovery, for good. Here, very evidently, enough quinine was not given during his illness nor continued after the acute attack to eliminate the parasites from the system. This case forcibly brings out the danger of withholding quinine or cassia beareana during the period of attack.

## APPENDIX A.

# BLACKWATER WITHOUT QUININE.

(1) In negroes who have never taken quinine (Ziemann, Deut. med. Woch., October 4, 1900, and Plehn (Journ. Trop. Med. and Hygiene, October, November, 1908).

(2) In a family affected with malaria in whom it came on whether quinine was given or not. In two it followed

quinine (Luzzato, Journ. Trop. Med., July 1, 1903).

(4) A case of "typical malarial attack with numerous parasites in the blood was complicated by a severe attack of hæmoglobinuria without quinine or any other remedy having been taken" (Dr. Albert Plehn (Berlin), in Journ. Trop. Med. and Hygiene, October 1, 1908, p. 296).

(5) Murri's case referred to by Plehn (in Journ. Trop. Med.

and Hygiene, October, 1, 1908, p. 297).

- (6) Plehn in same article, p. 300, refers to other authorities who observed blackwater in cases where quinine was excluded, and states that "this is the case in all native cases of blackwater."
- (7) Scheube says, "Blackwater fever is occasionally observed in patients who have not taken quinine immediately or for some time previously."

## APPENDIX B.

#### HÆMOGLOBINURIA.

Hæmoglobinuria is found in the following affections of man:—

- (1) Paroxysmal hæmoglobinuria (rare).
- (2) Congenital syphilis.

(3) Acquired syphilis.

- (4) Chlorate of potash poisoning, i.e., in excess doses.
- (5) Quinine poisoning (Koch, Barceilli), i.e., in excess doses.
- (6) Quinine in certain rare cases of suspectibility, even 1½ grain doses in 10 grains of ferri et quin. cit. (South African Med. Record, July 10, 1906); two cases of typhoid and one of leukæmia recorded by Scheube after taking quinine.
  - \*(7) Malignant tertian malaria without quinine.
  - \*(8) Malignant tertian malaria with quinine.
  - (9) Traumatism of the urinary passage.
  - (10) Carboluria.
  - (11) Jaundice.
- (12) Other poisons, as calichloricum, morchel, toluylendiamin, leuten, amyl nitrate (and antipyrin?).

Black urines are found in:-

- (1) Jaundice due to biliverdin, bilirubin, and other bile pigments.
  - (2) Blackwater fever.
  - (3) Carboluria.
  - (4) Chlorate of potash poisoning.

(5) Hæmatoporphyrinuria.

- (6) Melanuria (melanotic sarcoma)—brown on passing, but soon may be as black as ink.
- (7) Alkaptouria—normal colour on passing, but darkens on standing.
- (8) Ochronosis (blackening of tissues), in some cases blackens on standing.
  - (9) Carbon monoxide poisoning (methæmoglobin).
  - (10) Snake poisons.
    - \* These cases inclusive constitute BLACKWATER FEVER.

## APPENDIX C.

EXTRACTS TO BLACKWATER FEVER.

Stephens and Christophers, in British Central Africa (Reports to Royal Society), saw seven cases of Blackwater, all of which showed a malarial infection (based on fine pigmented mononuclear leucocytes and leucocyte variation), but only one showed during life the malarial parasite. In five cases urobilinuria was a constant phenomenon after the occurrence of hæmoglobinuria.

In twenty-eight cases as follows:—

Koch		,	17	cases,	there was	a quinine	history in	15
Ollwig			-		"	,,	,,	2
Malarial	Commi	ssion	8	,,	,,	"	,,	5

In 75 per cent. of these cases and 90 per cent. of the post mortems there was satisfactory evidence of malarial infection.

Blackwater fever is more prevalent during second and third years of residence.

In hæmoglobinuria after quinine and antipyrin in malaria, Vincent recommends 60 to 90 grains calcium chloride as a prophylactic. Vincent considers antipyrin a predisposing factor (Journ. Trop. Med. and Hygiene, February 15, 1908, p. 66).

The leaves of Combretum Raimbaultii is used by West African natives in cases of blackwater fever under the name of "Kimbelibah." A decoction is freely used (Journ. Trop. Med. and Hygiene, February 15, 1908, p. 67).

Quinine strongly advocated in the treatment by Brem (Journ. of Amer. Med. Assoc., December 15, 1906).

Deadrick advocates calcium chloride in treatment (Journ. Trop. Med. and Hygiene, December 16, 1907).

ABSTRACT EXTRACTS OF CASES OF BLACKWATER FEVER.

Journal of Tropical Medicine (April 1, 1903).—Case of blackwater fever treated with liquid ext. cassia beareana by H. Cooke (Lancet, March 21, 1903). He gave dose of calomel 3 grains, and then mxv. liq. ext. cass. bear., dose well diluted with water, and given every half hour at first and then every two hours. In forty-eight hours convalescent. In the Lancet, February 1, 1903, cassia beareana is described.

Journal of Tropical Medicine (April 15, 1903).—Otto Pause concludes blackwater fever results from a combination of malaria and some other foreign momentum (Zeitschrift für Hygiene und Infectionskrankheiten, vol. xlii., No. 1). This foreign material not necessarily quinine. The actual cause of the hæmocytolysis is undoubtedly malaria, but only when it comes into juxtaposition with the second and still unknown factor. Practically the fight against blackwater fever consists in combating malaria. Quinine prophylaxis only necessary for persons dwelling in notoriously malarial places. He recommends for this Koch's method, I gram of quinine every ninth or tenth day.

Journal of Tropical Medicine (June 1, 1903).—Walter Shropshire, of Yoakun, Texas, in Medical Record of May 16, 1903, in a report of 202 cases of blackwater fever, showed that of 61 cases treated without methylene blue or with less quinine than 5 grains per day, 26.2 per cent. died; while of 112 treated with 20 grains or over of quinine, 16.9 per cent. died. Of four treated with methylene blue, one died. Quinine not only lowered death-rate but also lowered the percentage of recurring paroxysms. His conclusions: (1) That the disease always occurred in persons suffering from repeated attacks of malaria; (2) that it nearly always followed one or more paroxysms of malaria at the proper time for its next exacerbation; (3) it had all the characteristics of malaria—chill, sweat, fever; (4) blood examination showed malarial hæmatozoa; (5) its habitat, that of the most violently malarious districts.

Re quinine as a cause, he says:—

Preponderance of evidence is against quinine as a cause; 29.4 per cent. physicians affirmed and 70.59 denied it. When quinine was suspended ... 73.8 per cent. recovered. When quinine was administered ... 83.1 Distinct recurrence after first blackwater fever in non-quininized patients occurred in 9.8 per cent. cases. Distinct recurrence after first blackwater fever in quininized patients occurred in 4.4 Of cases occurring alone from quinine (nil) . . . ... per cent.

Of cases occurring from malaria
without quinine ... ... 15 per cent.
Of cases occurring in which quinine
was said to aggravate ... 5.9 ,,
Of cases occurring in which quinine
was said not to aggravate ... 55.41 ,,

Treatment.—Shropshire advised 40 grains quinine daily until next period of exacerbation had passed; then stop for three or four days and then repeat in 20 to 30 grains every four to six days until five or six weeks passed without an attack. Attend to liver and bowels, also inject large doses hot water.

Moffat's case of congenital malaria is quoted in Jahrbuch der Praktischen Medizin (edited by Professor T. Schwalbe, Berlin). This, it may be remembered, was the case of an infant who, at the seventh week, developed malaria, the mother having contracted the disease in Africa. The infant was very anæmic at birth, and its blood contained the Plasmodium malaria of the malignant type.

# APPENDIX D.

#### STAINING.

Staining mixtures are numerous; a few need only be mentioned, as being the more important.

(1) Ehrlich's Triacid Stain.

Sat. aq. sol., orange G. ... 125 c.cm.
Sat. aq. sol. fuchsin cum
20 per cent. alcohol ... 125 ,,
Add whilst stirring conc.
aq. sol. methyl. green... 125 ,,
Absolute alcohol... 75 ,,

(2) (a) Romanowsky's method (for malarial parasites, &c.).

Conc. aq. sol. methyl. blue I part.

I per cent. aq. sol. eosin... 2 parts.

The mixture should be made immediately before use, and should not be filtered. The older the methylene blue the better the stain. (Limbeck.)

(2) (b) James ("Scientific Memoirs," Government of India, new series, No. 2) uses above stain as follows:—

Stock Solution A.

Pure medicinal methylene blue (Grübler) ... I gramme = 15 grains. Pure sodium carbonate  $\frac{1}{2}$  ,, =  $7\frac{1}{2}$  ,, Distilled water ... 100 cc. =  $3\frac{1}{2}$  oz.

Grind the blue in a mortar and add gradually the water. When solution made, add the sodium carbonate. Allow solution to stand in a hot sun for one or two days (or in incubator one week), until the blue has a red tinge by transmitted light.

Stock Solution B.

Eosinextra, B.A.(Grübler)  $\frac{1}{10}$  gramme =  $1\frac{1}{2}$  grains. Aq. distil. ... 100 cc. =  $3\frac{1}{2}$  02.

This must be kept in a dark place.

To make working solutions: Put 4 cc. of each into separate bottles, to each of which add 100 cc. distilled water. These form dilute solutions C and D.

To stain, take 10 cc. each of C and D (equal parts must be taken), and pour simultaneously over previously fixed slide in dish.

(2) (c) Leishman's modification of Romanowsky's stain (Brit. Med. Journ., September 21, 1901).

The formula for Leishman's stain is-

Crystalline methyl. blue,

eosin compound ... o'2 gramme.

Methyl. alcohol ... 100 cc.

Use small funnel with filter paper and pour the stain into the filter, and the freshly filtered fluid is dropped on to the film till evenly covered. After one minute's staining pure distilled water is dropped into the stain, drop by drop, until equal volume has been added; oscillate and allow to stand for five minutes. Pour off, wash into distilled water, and leave for one minute in distilled water. Dry in current of air; mount. (2) (d) Leishman's modification of Romanowsky's stain by Burroughs Wellcome and Co.'s "tabloids" I have found useful.

(3) Fenner's stain (Med. Ann., 1902).

"Two well-stoppered bottles of, say, 100 cc. capacity, each, are thoroughly cleansed, rinsed with distilled water, and dried in an oven. Into one bottle is put '5 gramme Grübler's medicinal methylene blue, and to this add 100 cc. Mark's absolute methylic alcohol, the stopper of the bottle being immediately replaced. Into the other bottle is placed 's gramme of Grübler's water-soluble eosin (yellow shade), and on it is poured 100 cc. of absolute methylic alcohol, and the stopper replaced at once. These two bottles may be kept as stock solutions, although if evenly mixed the stain will keep if properly protected. In mixing take a perfectly clean and absolutely dry stoppered dripping bottle, and 10 cc. of the methylene blue solution and 12.5 cc. of the eosin solution. Always see that all bottles are kept well stoppered, since evaporation will lead to concentration, and when stronger than 's per cent, the water with which the specimen is washed will cause a precipitate of the stain upon the cover-glass, and also because the absolute methylic alcohol will absorb water from the air, and so permit of the formation of a crystalline insoluble precipitate."

When Jenner's method is used no preliminary fixation is

(4) By a solution of Gentian Violet :-

Fix your film in a mixture of equal parts absolute alcohol and ether.

Add a few drops of a saturated alcoholic solution of gentian violet to a watch-glassful of water.

The parasite and leucocytes are deeply stained in half a minute: the red cells are either slightly yellowish-brown or unstained.

(5) By a solution of *Hæmatin* (Christophers' and Stevens' modification of Thier's formula):—

 R. Hæmatin ... ... ... ... ... ... 2 grammes.

 Alcohol (90 per cent.) ... ... ... 50 cc.

 Alum ... ... ... ... 50 grammes.

 Water ... ... ... 1,000 cc.

(The solution gains in rapidity of staining by keeping, and is very active when it has deposited a fine precipitate on the

sides of the bottle. Thier with his original formula subsequently works in alum; with the above the modifiers do not.)

(i.) Fix film; (ii.) leave in solution for five minutes or less according to age of solution; when film is a faint brown take it out.

Parasites and nuclei of leucocytes are well stained and nuclear networks are sharply defined, and pigment granules in cell body are distinct. The red cells are faintly greyishbrown, against which parasites stand out clearly. The method has the advantage that it does *not* stain vacuoles as methylene blue does.

(6) A New Blood Stain (Journ. Trop. Med., August 1, 1903). A modification of Jenner's stain:—

Solution 1: Unfiltered \( \frac{1}{2} \) per cent. solution of Jenner's powder in methylic alcohol.

Solution 2: One part Unna's polychrome methylic blue solution to 150 parts aqua distillata.

Method:

- (a) Five minims of Jenner's stain for one minute on coverglass specimen.
- (b) Then pour on above 10 minims polychrome methylic solution.
- (c) Agitate forceps so as to produce mixing and allow the combined stain to act for five minutes longer.
- (d) Work off with aqua distillata and allow some of this to remain on cover-glass for one minute with agitation of forceps.
- (e) Rapidly dip specimen into very diluted solution of acetic acid (I minim of 50 per cent. acetic acid solution to 10 oz. aqua) until it is of reddish or pinkish colour.
  - (f) Rinse in water.

(g) Dry (no heat or filter paper to be applied).

Result.—Parasite stained blue; chromatin stained bright carmine.

(7) An Easy Method of Microscropic Diagnosis of Malaria, by Dr. Reinhold Ruge (Deut. med. Woch., March, 1903).

Ruge discusses Ross's method given in Journ. Trop. Med., December, 1902. Ruge approves of Ross's plan, but makes the following suggestions: After preparing the specimen he treats them according to the well-known method of combining the fixing and extraction of the hæmoglobin (this he does, as he finds blood is often washed off in rinsing in Ross's method).

As, however, the layer of blood is very thick, placing them in a I per cent. solution formalin does not suffice, for before all hæmoglobin is extracted the preparation is fixed. He therefore adds \frac{1}{2} to I per cent. acetic acid to a watery solution of formalin, and increases the formalin to 2 per cent. (coml. formalin = 40 per cent.); thus he attains his result. cover-glass with thick layer of blood is inverted in a vessel filled with this acetic formalin solution, the hæmoglobin is extracted in a few minutes and the layer fixed to that extent that it can stand being well rinsed in water and then stained with Romanowsky's method. If in a hurry, one may even warm such preparations a little in Romanowsky's solution to expedite the process, and then differentiate in acidulated water without dissolving the layer. The sediments are easily washed out in alcohol. As the colour of the plasma is lessened by formalin it may be necessary to stain Romanowsky stained specimens with diluted Manson's solution, having previously washed off sediment; malarial rings are then distinct. These preparations will not be elegant as sediment deposits.

Quantitative Estimation of Hamoglobin:

Gower's hæmoglobinometer, in which you have two tubes of equal calibre, one being three-parts filled with picrocarmine gelatine, the colour of which corresponds to a 1 per cent. aqueous solution of normal blood. The other open tube has a scale 10 to 120 marked in it and receives the blood diluted with distilled water. A measured pipette sucks up 20 cc. blood, that is drawn and put into the open tube, which has a little distilled water put into it previously. Tube is shaken and then water put into it till the colour corresponds. The scale denotes the percentage of the normal.

# APPENDIX E.

# FEVERS IN INDIA.

Prophylaxis	(?) Pediculi (?); Bed-bug (?); Destruction of vermin; inoculation of sick. Culex (?)	Mosquito wire-netting to windows and doors and verandah; drainage; kerosenc oil to collections of water; quinine administration; mosquito nets.	As in the other forms of malaria, and keep liver in action.	Ouin.; salicyl.; mosquito netting.  Boil milk, water; cook vegetables; avoid oysters; incculation; latrines; segregation of "carriers".	Segregation; disinfection; inoculation; rat extermination; burning of infected articles.	Destruction of bed-bugs; destruction of in- fected house; fumigation; disinfection;	Mosquito wire-netting and prevention of collections of water.	Mosquito nets; wire-netting to houses; wearing gloves, putties, boots; atoxyl administration; drainage; isolation of sick; destruction of erocodiles.
Mode of spread	(?) Pediculi (?); Bed-bug (?); Culex (?)	Anopheles mosquito, infected with sexual forms from parasite in human blood	Anopheles infected with malignant tertian parasite	Stegomyia fasciata (?) Infected water, food, clothes, urine; human carriers; flies	and Yersin's Infected fleas from infected rats; (infected food, and contagion from souta in	pneumonic cases ?) Bite of bcd-bug	Culex; some Anopheles	Bite of infected Glossina palpalis and other Glossina
Cause	Liver derangement (?) Spirocheta obermeiri	Hæmamæbæ	Malignant tertian parasite	Germ or amœba (?) Eberth's bacillus	Kitasato's and Yersin's	Leishman-Donovan body	Filaria bancrofti	Trypanosome
Incubation period	(2)	8 days	(2)	I-7 days	3-5 ,,,	(2)	(2)	14 days
Fevers	(1) Simple continued * (2) Relapsing	(a) Malaria (b) Quartan (b) Benign tertian	(3) $(d)$ or $(4)$ Blackwaler	(5) Dengue ** (6) Typhoid	(7) Plague	(8) Kala-azar	(9) Filariasis	(10) Trypanosomiasis

<sup>\*</sup> With this must be remembered the "seven day fever." So called "low fever." I regard as due purely to hepatic derangement.

<sup>\*\*</sup> Scven day fever and some of the simple continued fevers are possibly modified types of dengue.

# APPENDIX E.—Continued.

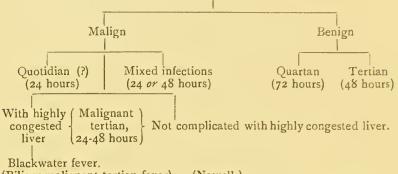
Prophylaxis	Vaccination; segregation of infected; disinfection.  Isolation; disinfection. Isolation of sick.  Isolation. Boil milk and water; provide latrines; protect food against flies; disinfect infected articles, &c.  Isolation of sick.  (Rare in India and have only seen one genuine case of acute Bright's disease.) Isolation (?). Isolation and disinfection of hands. Isolation; isolation; antitoxin. Disinfection; isolation. Disinfection; isolation.	n diagnosis.
Mode of spread	Aerial; and infected persons and clothes  Goat's milk and urine; cow's milk and urine; urine of infected dogs, sheep and goats; infected clothes and houses  Aerial and infected persons  Food (?) Insects (?)  Aerial.  Inculation  Infected persons or clothes  Infected persons or clothing  Infected persons and clothes  Fomites; aerial	also be met with, and have to be taken into consideration in diagnosis.
Cause	Bacillus albus variolæ  Not known Bacillus (?) Pfeiffer's bacillus Micrococcus melitensis  Diplococcus  Streptococcus erysipelatis Diplococcus intracellularis meningitidis Klebs-Löffler bacillus Streptococcus (?)	also be met with, and have to
Incubation	12-14 days 14 days 10-14 days 2-6 days (?)	These may a
Fevers	 rer rer opsy*	(26) Septicæmia (27) Pyæmia (28) Acute miliary tuber-

\* With this might be included BERI-BERI.

#### APPENDIX F.

#### CLASSIFICATION.





(Biliary malignant tertian fever) (Newell.)

Variety of parasite	Duration of develop- ment	Movement and size	Pigmentation	Number and forms of spores
(1) Benign or spring quartan	72 hours	Sluggish; nearly size of red blood corpuscles		6-12, "daisy" form.
(2) Benign or spring tertian	48 ,,	Very active, size of red corpuscles, or even larger		12-20, "sun- flower."
(3) Malignant tertian	48 ,,	Very active, very small	Very fine and collects in lumps	Irregularly formed heap. (Manson.)

Æstivo-autumnal Hæmosporidia differ from those of spring: (1) Being much smaller, and occupy only one-fourth to onefifth of the red corpuscles; (2) very active; (3) pigment consists of very fine granules; (4) rapid development, twentyfour to forty-eight hours; (5) certain special forms, e.g., crescents (diagnostic); (6) greater tendency to occupy internal organs than peripheral blood; (7) greater malignancy and resistance to quinine.

In Æstivo-autumnal Fever (malignant tertian) observe: (1) Some forms rapidly altering the red blood corpuscle, which becomes shrivelled up and "brassy"; (2) crescents (ovoid or fusiform)—pathognomonic; (3) some crescents become round and emit flagella (microgametes or spermoids).

#### APPENDIX G.

#### THE BLOOD.

				Normal numb	er Ratio
Red blood corpuscles (er	yth	rocytes)		5,000,000	0
White blood corpuscles				7,500,00	o I to 666.
D 1 1		Percentage co			blood corpuscles
Polynuclear				68 per c	ent.
Lymphocytes		• • •		25 ,,	
Large mononuclear	• • •	• • •	• • •	6 ,,	
Eosinophiles	• • •	• • •		Ι ,,	
				100	

#### ESTIMATION OF VOLUME OF BLOOD.

Vierordt's Second Method.—A measured quantity of blood is taken (A), and the number (B) of red blood corpuscles in it estimated. A same quantity of blood is drawn after a sufficient interval in order to allow amount previously taken in fluid to be made up. Let c = number of red corpuscles in this second sample. If x = volume of blood, then,

$$\times = \frac{A C}{B-C}$$

The enumeration of corpuscles and platelets by Limbeck's method.

(1) The Enumeration of Corpuscles and Platelets:-

In all the methods a small quantity of blood is taken and mixed uniformly with some preservative fluid, with the addition of a dye to stain the white corpuscles. Many fluids are used; the chief are:—

#### Pacini's Solution :-

Mercuric chloride	 	 	2.0
Sodium chlorate	 	 	4.0
Glycerine	 	 	26.0
Aq. dist	 	 	226.0

One part to be mixed with three parts before use.

#### Gower's Solution :-

(a)	Sodium sulphate	 	 	6.3
	Acetic acid	 * * *	 	3.6
	Ag. dist	 	 	117.0

(b) A water solution of sodium sulphate of specific gravity 1025.

#### Toissou's Solution :-

```
      Glyc.
      ...
      ...
      30 cc.

      Pure sodium sulphate
      ...
      8 grains.

      Sodium chloride
      ...
      ...
      1 grain.

      Methyl violet, 5B
      ...
      ...
      ...
      ...
      ...
      ...

      Aq. dist.
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(Stains the nuclei of white corpuscles.)

It is necessary to use a fluid which preserves the white cells, but breaks up the red cells, if we are to estimate the number of white blood corpuscles satisfactorily. The best fluid for this is a '3 to '5 per cent. solution of acetic acid (Thoma), to which a small quantity of aniline dye may be added.

It is usual, in making a differential count of the white corpuscles, to form an estimate of the relative proportion of the different white cells in a dried microscopic specimen, and then to calculate the actual numbers from an enumeration of the total number of white corpuscles made in the ordinary way. Eltzholz uses solutions which stain the granular forms of white corpuscles. These solutions are:—

#### Solution A:-

```
Eosin, 2 per cent. ... ... ... 7 parts.

Glyc. ... ... ... ... 45 ,,

Aq. dist. ... ... ... ... 55 ,,

Solution B:—

Conc. aq. sol. gent. violet ... ... 5-6 minims.

Alcohol ... ... ... ... ... I minim.
```

Blood is drawn up in a Thoma-Zeiss white corpuscle pipette to the mark I or I'5, and then solution A until half the bulb is filled. The bulb is well shaken up for three or four minutes, and the solution B sucked up until the mark is reached. The different stained cells are then counted under the microscope.

The same instrument can be used for counting either red or white cells, but in the case of the former the blood is diluted 100 to 200 times, whilst as white cells are much fewer the dilution in their case is only 10 to 20 times. Many instruments are used, the following being the chief:—

- (1) Hayem's apparatus.
- (2) Gower's hæmacytometer.
- (3) Mallassez's apparatus.
- (4) Thoma-Zeiss's apparatus.
- (5) Alferow's hæmacytometer.

(6) Mallassez's new "counting chamber." Gower's and Thoma-Zeiss's are most used.

Gower's instrument is like Hayem's, only the square divisions are marked on the slide instead of being on the microscope, and the side of a square is  $\frac{1}{10}$  mm. instead of  $\frac{1}{5}$  mm. (Hayem's); the depth is the same, viz.,  $\frac{1}{5}$  mm. There are two pipettes of 995 mm. and 5 mm. capacity respectively, so that the number of corpuscles found in a square has to be multiplied by 100,000 to get the number in one cubic millimetre of blood.

Thoma-Zeiss's apparatus consists of a capillary tube, 10 cm. long, which enlarges into an ovoid bulb, containing a freely movable glass bead to facilitate mixing. Below the bulb are the marks '5 and 1'0, whilst above is the mark 101. There is a counting space, which consists of a glass frame, in which a circle is cut out, glued to a slide; in the basin so formed is a small circular glass disc with small squares engraved in its centre. The difference in height between the frame and the disc is exactly I mm., and the side of one of the squares is  $\frac{1}{20}$  mm. The counting is done as follows: Blood is sucked up to 5 or 1, and the diluting fluid to 101. (The diluting fluid is 10 per cent. sulphate of soda solution, or some such fluid as will not destroy the corpuscles. When the blood is drawn up to I and diluting fluid up to IOI you have a dilution of 100.) The tube is shaken, a drop of the mixture is placed in the glass disc, and a thick cover-glass put over it. Allow to stand for a few minutes, then count the number of corpuscles in sets of the four small squares, as sixteen of these small squares form one large square. (Each square has a capacity of  $\frac{1}{400}$  mm.)

No. corpuscles per mm. =  $\frac{\text{No. counted} \times 4,000 \times \text{by amount of dilution.}}{\text{No. of small squares counted.}}$ 

(2) Examination of Corpuscles.—This may be done either in the fresh or dried state. The former is useful and alone may be sufficient for the diagnosis of a case of malaria or relapsing fever, and in the former case a warm stage is preferable, and in the latter the hanging drop. In the examination of dried specimens certain stains are requisite for differential diagnosis. Before staining, blood preparations are sometimes also specially "fixed." Benares (Deut. med. Woch., 1894, p. 572)

advises the use of 10 per cent. formol solution diluted in nine times its amount of alcohol, the preparation being kept in this for one minute and then, without drying, put into the staining mixture. The hæmoglobin of the red cells may be fixed by heating on a copper plate for ten to twelve hours, at temperature of 110° to 130° C., or by placing the dried specimen in a solution of equal parts of ether and alcohol for twenty minutes. When fixed the specimen is placed in a staining mixture of acid, basic, and neutral dyes.

The acid dyes are those which have an acid as the colouring principle, e.g., ammonia picrate, eosin, methyl violet, &c.

The basic dyes have a colouring base combined with an indifferent acid, e.g., fuchsin, Bismarck brown, methylene blue, &c.

The neutral dyes are composed of an acid dye with a base, e.g., picrate of rosanilin.

Osmotic Relations of the Blood.—Limbeck says:—

"Every cell, according to the substance dissolved in it, has certain osmotic powers, and if no exchange is going on between it and the fluid around it the two must be in osmotic equilibrium. The sum of these powers is called 'turgor,' and De Vries was the first to estimate it in plant-cells. His method was to find the concentrations of different salt solutions which had the same 'turgor' as the cells. He gave the name 'isotonic' to such a solution."

In blood thrown into water the corpuscles disintegrate, but this does not occur if a certain concentrated saline solution be used instead of water. That solution which is just sufficient to prevent the egress of hæmoglobin from the corpuscles is "isotonic" to the corpuscles, and represents their 'tone.'"

Morphology.—The red corpuscles are circular non-nucleated discs. On a slide they arrange themselves in rouleaux. Outside the body they take up one stain out of a mixture of aniline dyes, e.g., out of a mixture of methyl blue and eosin the eosin only is taken up (monochromatophile). In certain pathological states this selective power is lost, and several stains may be taken up (polychromatophile). Endoglobular changes in the corpuscles (such as the disappearance of the hæmoglobin to the periphery of the corpuscle with certain amæboid movements) and the formation of poikilocytes (knobs or points sprouting out from the corpuscles, giving it a poly-

morphous appearance) are regarded as signs of degeneration or necrosis of the corpuscles. When blood is being made up, as in severe anæmias, there are often found nucleated red blood corpuscles, which are signs of regeneration of the blood. Ehrlich divides these into two groups, viz., the normoblasts and the megaloblasts.

Normoblasts are nucleated red blood corpuscles of the size of the normal corpuscle, and which, when stained, have a characteristic appearance—the body of the cell takes up the acid dye, and the central nucleus takes up the basic dye. The nucleus, though usually single, may be two or three.

The megaloblasts are two to four times as large as normoblasts, coarser, and richer in hæmoglobin. They are said not to occur in the blood of adult healthy men, or animals but in embryo (Ehrlich). The nucleus is said to degenerate in the cell.

#### Normal Number of Red Corpuscles:-

Average in man ... 5,000,000 per mm.

,, females ... 4,500,000 ,,

If increased above average = polycythæmia.

If diminished below average = oligocythæmia (= anæmia).

There is a relatively high number immediately after birth. Iron exercises a favourable influence on the number of corpuscles in disease, as also in certain cases does arsenic; mercury to a less extent. Lead has the opposite effect, causing diminution in the number of corpuscles. In certain pathological conditions (certain fevers) and in certain poisons (pyrogallol) there is also a diminished number of red corpuscles.

#### WHITE BLOOD CORPUSCLES :-

- (a) Non-granular.
- (b) Granular.
- (a) Non-granular:—
  - (1) Small lymphocytes (younger form of the large mononuclear)—present to extent of 25 per cent. of the leucocytes in the blood.
  - (2) Large mononuclear lymphocytes—present to extent of 4 per cent. Phagocytic.
  - (3) Transitional cells.

(b) Granular:—

(1) Polymorphonuclear. Nuclei 3-6. 70 per cent. of normal leucocyte count. Increased in inflammatory diseases and decreased in long-continued fevers, pernicious anæmia, &c. Pus consists mostly of polymorphonuclears. Granules stain

with acid aniline dyes. Phagocytic.

(2) Eosinophiles in size between large mononuclear and polymorphonuclear. Granules of protoplasm stain with acid aniline dyes and have special affinity for eosin; nucleus single or double, generally horseshoe-shaped and eccentric, and does not stain so deeply as that of polymorphonuclears. Not phagocytic; constitute I per cent. of normal leucocytes. Relatively numerous up to age of 14 years and may be as much as 11 per cent. Increased in asthma, skin diseases, helminthiasis, &c. Decreased in croupous pneumonia.

(3) Myelocytes (narrow cells). Abnormal constituent. Basophile. Nucleus single and indented.

(4) Mast cell—granular basophiles. Abnormal. Dense granules in protoplasm obscure the nucleus. Rare.

Mononuclear cells are cells two or three times the size of red blood corpuscles, with large oval, generally eccentric nucleus, staining feebly and with relatively large amount of protoplasm, free of granules, weakly basophile. According to Ehrlich they are transformed in the blood into transitionals. These mononoclear cells take up pigment in malaria and blackwater fever.

The richness of the blood in hamoglobin may be estimated by:—

(1) Gower's hæmoglobinometer.

(2) The spectroscope.

(3) Tallqvists' Hæmoglobin Scale Books.

(4) Dr. Arthur Hall's Rotary Hæmoglobinometer. (British Medical Fournal, March 27, 1909, p. 794.)

#### APPENDIX H.

ANATOMY OF ADULT FEMALE MOSQUITO.

Exoskeleton = Head, thorax, and abdomen.

- (1) Head.—Great portion taken up by the large eyes, which meet inferiorly in the middle line. In the space between the eyes are the large basal joints of the antennæ. Under the origin of the antennæ are the combined clypeus and labrum, with the proboscis.
- (2) Thorax. Three segments (pro-, meso-, and meta-thorax). The mesothorax is the largest.

Each segment has a dorsal piece or notum, a ventral piece or sternum, and a lateral piece or pleuron.

- (a) Prothorax.—Notum undeveloped; on either side of base of neck are two freely movable plates (patagia).
- (b) Mesothorax.—Has a large ovoid scutum. Posterior to this is a thick, transverse ridge (scutellum). Behind this, and forming roof of thorax behind the wings, is a large plate to which the posterior portion of the great antero-posterior wing muscle is attached. The mesothorax forms two large surfaces behind the first pair of legs, and projects laterally above the middle coxa. In the pleuron of the mesothorax is the largest spiracle of the body (the first thoracic stigma).

(c) Metathorax.—Has a large spiracle—the second thoracic stigma.

(3) Abdomen.—Eight segments, each made up of a tergum and sternum, connected laterally by a pleural membrane. The pleural membrane continues unbroken throughout the length of abdomen, and carries one abdominal spiracle opposite each segment. From last segment project two flap-like processes for the deposition of ova.

Wings arise from mesothorax. Not directly associated

with wing muscles on thorax.

Legs.—One from each thoracic segment. The proximal joint is the coxa. Between this and the femur is the small trochanter. There are also tibiæ and tarsi.

#### ALIMENTARY CANAL consists of:-

(1)	Mouth		,	
(2)	Pharynx with pumping organ			The Fore Gut.
3)	Œsophagus			. The PORE Got.
(4)	Œsophageal diverticula		)	
(5)	The homologue of the prov	entricu	lus \	
(6)	The stomach			The MID GUT.
(7)	The pylorus		)	
(8)	The pyloric dilatation		)	
(9)	The small intestine			The Heart Com
(10)	The colon			The HIND GUT.
(11)	The rectum with rectal papilla	æ	)	

The pharynx is lined throughout with chitin, and passes upwards and backwards through the ganglionic ring formed by the supra- and infra-œsophageal ganglion. Narrow at first, it widens posteriorly into the pumping organ. The walls of this last are formed of three large and thick chitinous plates—one on each side and one superiorly. In each plate are inserted powerful muscles. It leads into the œsophagus—a thin-walled, dilated sac.

The diverticula of the esophagus contain air, and extend into the abdomen.

A fold of the fore gut into the middle gut represents a homologue of the proventriculus (no true proventriculus as in insects).

Mid Gut extends from proventricular fold to origin of Malpighian tubes. It is narrow anteriorly and dilated posteriorly. There are no cæcal appendages. Anterior narrow part is in thorax; posterior part, when fully filled with blood, is in abdomen.

Hind Gut passes from pylorus to anus. Immediately behind pylorus is a dilatation into which open five Malpighian tubules. From the dilatation is small intestine opening into larger tube, colon, which constricts before opening into rectum, which has six papillæ and opens in the anus above the gynæcophoric canal.

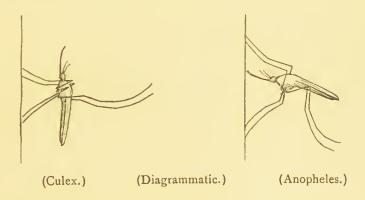
Salivary Glands.—Six tubular acini on each side. On each side they lie one above the other in the long axis of the body, anterior ends close against prosternum, where ducts from each unite to form a single duct. The duct of each side passes into the neck and lies close to the nerve cords passing between thoracic and central ganglia. Beneath, and in con-

tact with the lower surface of the subæsophageal ganglion, the ducts of each side unite to form a common salivary duct which enters first portion of the alimentary canal close to the base of the proboscis.

TRACHEAL System.—Respiration is carried on by tracheæ. These arise from external openings—spiracles—and end in minute capillaries in the tissues of the insect. There is no development of air sacs as in insects. The tracheæ ramify and extend inwards, anteriorly and posteriorly.

VASCULAR SYSTEM is represented by a dorsal vessel (heart) and a prolongation forward (aorta), the blood circulating chiefly in blood spaces, muscles and viscera.

On either side of the dorsal vessel are large pericardial cells throughout the whole extent of it. These are the largest cells in the mosquito (30 to 50  $\mu$  long).



NERVOUS SYSTEM :-

- (1) Supra- and infra-œsophageal ganglia with the commissures around pharynx.
  - (2) Thoracic—gives nerves to limbs and joins (1) and (3).
  - (3) Abdominal—below junction of oviducts.

REPRODUCTIVE SYSTEM:

- (1) Ovaries.
- (2) Oviducts and common oviduct.
- (3) Mucous gland and duct.
- (4) Spermathecæ and ducts.

Ovaries in the newly hatched mosquito lie in the fourth and fifth abdominal segments, but on enlargement occupy the whole of the posterior abdomen. Oviducts—muscular tubes—join and open out beneath anus. Spermatheca, a chitinous

sac, holds the spermatozoa and opens into the common oviduct; here the mucous gland also opens.

Fat bodies are found under the cuticle, among organs and muscles, but one large mass found over the compound thoracic ganglion.

CULEX differs from Anopheles in having:-

(1) More robust exoskeleton.

(2) Tubular salivary glands (Anopheles are sacculated).

Some Points of Distinction between Anopheles and Culex.

	Anopheles	Culex
(1) Ends of sa- livary glands	Dilated	Same size throughout.
(2) Legs (3) Palpi and proboscis	Double length of body Equal length	Same length as whole of body. Male has palpi longer than proboscis; female has palpi much shorter than proboscis.
(4) Wings (5) Abdomen	Spotted With bristles (three exceptions have scales)	Unspotted. With scales.
(6) Size (7) Manner of resting (vide fig.)	Small	Large. Abdomen parallel to or at an acute angle to resting surface, third pair legs taken over the back.
(8) Receptacu-		The female has three such.
(9) Breeding- place	Stagnant waters, as in puddles or small collections of water	Running waters, rain-water- barrels, ponds, &c.
(10) Deposition of eggs	3 to 20, in short rows, which float horizontally	200 to 300, in compact heaps, in which the eggs stand perpendicularly.
(11) Larvæ	Breathing stigmata on back (no syphon). Lie horizontally beneath sur- face of water	Stigmata in fore end of a long tube—syphon. Point of syphon touches water, head hangs down.

- (3) Duct of the acinus same diameter throughout (that of Anopheles becomes larger at termination).
  - (4) Three receptacula seminis (Anopheles have one). Mosquitoes differ from many insects in—

(1) Having five Malpighian tubules.

- (2) No true proventriculus.
- (3) No cæcal appendages.
- (4) No development of large or multiple air sacs.

THE BITING APPARATUS of the mosquito is hidden within a sheath (lower lip or labium) which ends in an olive termination, and consists of SIX PIECES, viz.:—

(1) The lip (labium) ending in a sharp oblique point.

(2) The epipharynx or hypopharynx (puncturing organ).

(3) Two mandibles.

(4) Two maxillæ—ending in a servated extremity. When biting, the sheath does not penetrate the skin, but bends backwards towards the thorax. The saliva goes through the lumen of the hypopharynx, while the blood is sucked up in the groove of the labium.

All the above make up the proboscis, which is longer than the antennæ. On the right and left, next to the proboscis, are the straight five-jointed palpi, the final joint of which is thickened in the male.

#### CARRIERS OF MALARIA.

Malaria is carried by Anopheles.

The group of small dark mosquitoes with unbanded legs, A. christophersi, A. jeyporensis, A. listonii, A. culicifacies, A. indica, appear to be chief carriers of malaria, and are associated with high "endemic index" areas. A. funestus is the carrier of malaria in many parts of Tropical Africa.

A. stephensi, A. theobaldi, A. barbirostris, A. fuliginosus can also carry malaria.

Myzomyia funesta, M. superpicta, M. paludis transmit it in West Africa, and Nyssorhynchus lutzi in Brazil.

Many others in other places. It would appear that the entire genus *Anopheles* can transmit malaria to man, but this has not been proved by all, and certainly *A. rossii* was found not to do so.

True Anopheles are distinguished by the absence of scales on thorax and abdomen, and by rather densely scaled wings with lanceolate scales.

Myzomyia have "usually a few narrow-curved thoracic scales projecting over the head, whilst the wing scales are much smaller in proportion, and the wings more uniformly spotted, always so along the costa" (Braun).

A STRAIGHT PROBOSCIS and PALPI as LONG, or nearly as long, as the PROBOSCIS are found in the females of ANOPHELINE MOSQUITOES ONLY—characteristic.

Genus			Thorax				Abdome	n	
Anopheles		Curved	hair-like	scales	***	Curved	hair-like	scales.	
Myzomyia		2.2	>>	,,		,,	, ,	,,	
Myzorhynch	215	,,	,,	, ,	***		les on	ventral :	sur-
λ7	7	77		:	1			al segme	
Nyssorhync	nus	Marion	w-curved	spinare	scares	Dorsum			
								d hair t	ufts
						projec	ting late	erally.	

#### Development of the Malaria Parasite.

Spores taken into the intestines of the Anopheles mature rapidly, and the filamentous microgametes penetrate into the macrogametes. The copula thus formed first becomes a motile fusiform body ("vermicle" or "oökinet") which bores into the intestinal wall of the mosquito's stomach. A delicate covering develops on the surface of the oökinet, which becomes round, and thus the occyst is formed. By a process of cell and nuclear division a number of mononuclear polyphedral cells are formed in the oöcyst. These are the sporoblasts. They become the sporozoites by a cell division of the nucleus in each sporoblast. The sporozoites become small elongated bodies, pointed at each end. When the sporozoites are provided with an elongated nucleus they become detached from the residual body. (There may be 500 to 10,000 sporozoites in an occvst). When the mature occyst bursts it discharges the sporozoites into the body cavity of the mosquito. They are distributed by the circulation of the blood and soon reach the salivary glands. Sporozoites possess specific movement and are discharged with the saliva on biting man. In the blood of man they multiply by schizogony until their number is sufficient to produce the first attack of "fever." Thus the sexual development (sporogony) occurs in the body of the Anopheles and the asexual development (schizogony) in the blood of man. As the adult stage of the parasite is passed in mosquitoes these are the definite hosts, and man the intermediary host. Besides the schizogony observed in man, certain other forms of the parasite are occasionally met with, viz.

crescents, spheres, and flagella. Manson and Ross demonstrated that crescents taken up by mosquitoes from man's blood turned into spheres, and half of them transformed into polymites. Flagella have been observed to penetrate spheres. Thus "flagella" are microgametes, and the spheres partly macrogametes and partly polymites, which are microgametocytes.

#### DIAGNOSIS OF MALARIA.

The presence of parasites makes diagnosis certain. If parasites are not present, and whether quinine has been taken or not, the absence of parasites is not proof against presence of malarial infection. Much quinine destroys parasites in peripheral blood. Under these circumstances, in the absence of parasites, how can diagnosis of malaria be made? As follows:—

(1) Variations in leucocyte count follows closely variations of temperature. The diminution is constant throughout the temperature curve even below 2,000 per c.mm.

(2) There is an increase in the large mononuclear constituents in the leucocyte count, and a decrease in the polynuclear and small mononuclear. [This change being most marked in the period of apyrexia (Christophers and Stephens).] Over 15 per cent. increase shows recent malarial infection.

(3) "Immediately succeeding the fall in temperature, the mononuclear leucocytes increase to such an extent as to equal or outnumber the polynuclear. Then the increase falls away until there is a sudden interruption due to changes coincident with the ensuing febrile attack" (Christophers and Stephens). If the temperature does not rise, there is a gradual fall in the number of mononuclears till normal proportion is reached. There is, in regular curves of temperature, a preponderance of mononuclear leucocytes with the occurrence of large forms of parasites, while with small forms there is a polynuclear increase.

Christophers and Stephens believe that the mononuclear increase may continue some time after subsidence of fever, with a possible relation to immunity and continued infection.

(4) The occurrence of pigmented leucocytes is diagnostic. The mononuclear leucocytes contain one or two lumps and

10 to 30 fine grains of pigment in the cell-body. This gives definite indication, in the absence of a parasite, of a recent infection of malaria.

Pigment may also be found in the polynuclear cells, but such would not alone justify a diagnosis of malaria, and the absence of pigment in any of the leucocytes (mononuclear included) would not exclude malaria. Cases have occurred where mononuclears showed no pigment in the peripheral blood (probably due to quinine intake), but those in spleen blood were found pigmented.

#### APPENDIX I.

THE PHARMACOLOGY AND CHEMICO-PHYSIOLOGICAL STUDY OF QUININE AND ITS RELATION TO THE TREATMENT OF MALARIAL FEVERS, INCLUDING BLACKWATER FEVER.

The following points have been dealt by a number of investigators, of whom Kleine, Mariani, Flamini, and Schmitz are the pioneers, viz.:—

(1) Finding out the suitable dose which is required for the treatment of malaria in the quickest possible way.

(2) Finding out the most appropriate way of administering the drug (by mouth, rectum, or hypodermically).

(3) Finding out the most suitable preparation of quinine.

(4) Explanation of the causative relation between quinine and blackwater fever.

To solve these questions clinical observations and chemicophysiological observations are both necessary. Drs. G. Giemsa and H. Schamanes have recently taken up the solution of these problems, and subjected a large number of persons to experiments. At the outset they state that the action of the alkaloid is not the same in different individuals. Whilst most observers studied the action of quinine in healthy individuals Giemsa, and Schamanes systematically examined the effect of quinine on malarial cases in the Leeman's Hospital, where the different preparations of quinine were studied as to their effect on malaria parasites, and their therapeutic value judged.

The absorption, elimination, and pharmacological action of quinine were studied according to the following methods:—

- (1) After daily 1 gramme doses of quinine salt dissolved in water administered by the mouth.
- (2) After 5 doses of 0.2 gramme of the same salt daily (in the course of ten hours).
  - (3) After one dose of free quinine (base) by the mouth.
- (4) After subcutaneous injection of quinine solutions of different kinds.
  - (5) After administration of quinine by the rectum.

Chemical Property and Special Test of the Alkaloid.—Quinine belongs to a group of alkaloids, each of which is a powerful poison containing an organic base (alkaline in character) combined with an organic acid found in many plants. A free base is amorphous and, as a rule, less soluble in water but freely soluble in alcohol and different ethereal solutions; when combined with acids it forms a crystalline salt. The salt, which is easily soluble in water, is preferred for therapeutic purposes.

The examination of its physical properties consists in the estimation of its optical property as well as finding out its rotation power. To identify it chemically special reactions are resorted to. Quinine, as well as the most allied compounds, such as, chitenin, chinidin, iochinin, nictrin, give a special characteristic reaction, the so-called Thallelo-Quinine REACTION, which separates them from alkaloids belonging to other groups. To get this reaction we add a small quantity of quinine salt to 5 cc. of water in a test-tube and gradually add freshly prepared bromine water till a yellow colour appears; I to 2 cc. of ammonia is then added when this becomes green coloured. This colorimetric examination of quinine is not suitable when we have the drug in weak solution in the urine, the reason being that in urine there is present a large quantity of an organic substance (urea) on which bromine acts energetically, and so other special tests are required for its detection in the urine. Of these the most suitable is the Potassium Hydrargyrum Argentum IODIDE TEST which gives a reaction in acid urines even when quinine is present in so weak a dilution as I in 200,000 (I: 200,000).

(I.) Qualitative Examination for Quinine:—

- (a) Fluorescence.—This gives a reaction in dilution of 1 in 200,000, but it has several drawbacks.
- (b) Acid Solution of Potassium Mercury Silver Iodide.—Its limit is 1 in 20,200.
- (c) Thalleirochinin Reaction.—Is sensitive up to dilution 1 in 7,500.
  - (II.) Quantitative Estimation of Quinine:-
  - (a) Phospho-molybdic acid method.
  - (b) Picrate method after Kleine.
  - (c) Gaglio's method.
  - (d) Ethyl ether method.

[Giemsa and Schamanes have come to the conclusion that the various supposed derivative products of quinine, as described by several workers, such as *chitenine*, &c., are not found in the urine.]

Absorption and Relation of Quinine in the Organism and its Excretion.—Most authors are agreed that the quantity of quinine excreted in the urine corresponds to the amount of the drug absorbed in the circulation. Some of the quinine taken internally is excreted with the fæces and a portion is destroyed in the system. Mariani says that the excretion co-efficient is in strict relation with the absorption on the one side and excretory power of the excretory organs on the other side, but conversely related to the quantity broken up in the system. We do not possess means of determining the amount of quinine broken up by the organism, and therefore, strictly speaking, do not know if the absorption of quinine by the system corresponds to the excretion. However, Giemsa and Schamanes found the amount excreted with the fæces to be very small indeed, so that it may be practically left out of consideration.

Regarding results of observations as to the ways of administrating quinine they found:—

(1) By the mouth:-

(a) Absorption.—After giving quinine in its most soluble form by the mouth the first trace of quinine appears, according to Lewar, in thirteen to seventeen minutes. When given in an insoluble form it is found in twenty-five to thirty minutes when taken on an empty stomach. This observation shows that the stomach takes the greatest share in the absorption

of quinine, but it is also to be noted that quinine takes a relatively shorter time to reach the kidney from the stomach.

Solubility of Quinine in Stomach Juice :-

Drs. Giesma and Schamanes ... 19.6 per cent.
Flamini ... ... 19.0 and 20.94 per cent.

Kirner and Zhau found greatest portion excreted in six hours, and Garafold in half hour to four hours. Mariani found greatest excretion is in six hours, and in case of full stomach ten to twelve hours. When quinine is given with food, according to Mariani, a large part is absorbed by the small intestine. The greatest portion of quinine which is absorbed within the first six hours is absorbed by the stomach.

Mariani removed on one occasion 100 cc. and on another 130 cc. of bile by means of a catheter from a cholecystitis case which had been operated on and had been previously treated with quinine. He found that the first part contained 0.007 gramme, and the second 0.004 gramme quinine. Flamini found that by treating quinine tannate with bile 6 per cent. of the quinine was dissolved. According to Flamini, bile dissolves 60 per cent., and according to Giemsa and Schamanes, 59.63 per cent. quinine.

Subjective symptoms give proof of the power of the small intestine to absorb quinine. Thus in Giemsa and Schamanes' experiments, ringing in the ear, general uneasiness and shaking came on three to six hours after quinine on an empty stomach, and between sixteen to nineteen hours given on a full stomach.

In application by clysma, the absorption of quinine is very small—5.7 per cent. by Giemsa and Schamanes. The small quantity absorbed by the large intestine is ascribed to the want of active movement of the intestine.

Excretion by the faces is very small (Kerner, a trace; Mariani, 2.67 to 3.13 per cent.; Giemsa and Schamanes, a trace only).

RELATION OF QUININE (ABSORBED) TO THE BLOOD.—Giesma and Schamanes made a series of experiments in vitro and on animals (mainly dogs) to find out how much quinine is found in the blood, and in what physical and chemical combinations it is found there. They examined the effects of saturated solutions of different salts of quinine on the serum of pig's blood, and for this purpose 5 cc. of the

serum was mixed with 5 cc. of a solution of the quinine salt in a test-tube. Here is a summary of their results observed in clear serum:—

Quinine salt		Relation of	of solution containing	Changes noticed		
		solubility	water-free quinine	At once	After 24 hours	
Quinin	e hydrochlor	Grammes I:36	Grammes 0.117	Marked precipitate	More marked precipitate	
"	bihydrochlor	I: 2	1.814	Slightly opalescent	Opalescent, gelatine-like	
,,	lacticum	1.19:10	0.452	Opalescent	Cloudiness	
"	dihyd. carbon	I: 2	1.480	Clear fluid	Opalescent, gelatinous	
,,	bisulphuric crystal	1:9	0.870	Marked precipitate	More marked precipitate	

Experiments with human serum gave similar results.

Experiments were made to determine the action of quinine on erythrocytes in relation to hæmoglobin, but the experiments gave no definite result as to whether a definite chemical combination of quinine with the blood pigment could be formed.

Experiments were made on animals to find out the quantity of quinine found in the blood after its administration by the mouth. In one of three experiments they found a very small quantity of quinine in the blood and none in the corpuscles. They conclude: (1) Only a trace can be found in the blood at any given moment; (2) that the blood contains less than 0.000018 gramme of quinine; (3) that practically the alkaloid is only found in the serum and not in the blood corpuscles; (4) that in consideration of the remarkably small quantity (demonstrated by pot. merc. silver iodide) of quinine in the blood it is questionable whether the assertion that the destruction of malaria parasites goes on in the peripheral vessels is true. [In this connection it is to be noted that paramecia became paralyzed by the application of quinine I in 20,000 in five minutes and became motionless after two hours (Binz). Turbellaria dies after the application of a solution of I in 100,000 in four hours. Possibly the

poisonous action of the alkaloid on the malaria parasite requires to be in a little stronger solution.] (5) That other experiments by themselves show that when a very small quantity of quinine—but a large quantity relatively to the blood—gets into certain organs, e.g., kidneys, it is probable that the destruction of the parasites takes place preferably in this organ.

RELATION OF QUININE TO ORGANS.— Three dogs were given large lethal doses, and during intoxication were killed by opening the carotids. Efforts to find amount of quinine in the organs were frustrated by the small quantities found.

In the experiments they found there was slight storing up of quinine in the brain, liver, spleen, kidneys and accessory kidney. Quinine disappears quickly from all the organs with the exception of kidney and accessory kidney. The liver also appears to retain a trace of quinine.

So far no investigations prove whether the destruction of quinine takes place in the liver (Mariani and Vegar), or whether in other organs, or partly in one and be completed in another.

EXCRETION OF QUININE IN THE URINE.—Kleine, Mariani, and Schmitz have lucidly worked out the question whether quinine is excreted as such in the urine or as some changed product.

Kerner thought quinine introduced by the mouth is excreted partly as quinine and partly as its changed product, which he called dihydroxylchinin ( $C_{12}H_{26}N_2O_4$ ), which is changed by oxidation to chitenin. Others think quinine is excreted without undergoing any change. Kleine gives the following figures when quinine is taken in the morning on an empty stomach:—

Dose of quinine	Excretion of water- free quinine	Corresponding quinine muriate	Relation to administered quinine
2 grs. quin. hyd 2 ,, ,, 2 ,, ,, 1 gr. ,, 1 ,, ,,	0.4140 gr. 0.3220 ,, 0.1580 ,, 0.2230 ,, 0.2250 ,,	0.5067 gr. 0.3941 ,, 0.19349 ,, 	25'34 per cent. 19'71 ,, 9'69 ,, 27'54 per cent.

The average of the excreted quantity of quinine within twenty-four hours after introduction by the mouth is 21.91 per cent.

Mariani gives the following table with regard to the excretion when quinine is taken on an empty stomach:—

Dose and variety of the quinine		Excretion (in one day), water-free quinine	Excretion in two days	
ī.	ı gr. quin. bihydrate	0.1728 gr. = 23.09 per cent.	0.0818 gr. 10.93 per cent.	
II.		0.1000 '' = 15.56 ''	_	
III.		0.2880 ,, = 34.89 ,,	0.0650 gr. 7.90 per cent.	
IV.		0.1840 " = 50.42 "	0.0340 ,, 4.11 ,,	
V.		0.2240 ,, = 29.90 ,,	0.0240 ,, 7.61 ,,	
VI.		0.1820 " = 51.20 "	0.0230 " 6.18 "	
VII.		0.3140 ,, = 36.62 ,,	_	

The average being in the first day 24.70 and in second day 7.37 per cent.

Flamini gives a table when 2 grains of quinine tannate is taken, his average being 42 per cent.; in chocolate the average is 40 per cent.; Schmitz averages 28.7 per cent. within forty-eight hours—19.5 per cent. in first twenty-four hours and 9.2 per cent in the second twenty-four hours.

The average of quantitative experiments by Drs. Giemsa and Schamanes is:—

	Excretion in the Urine				
Daily quinine dose in tablets	In 24 hours after introduction	In 72 hours after introduction			
gr. quin. hydro. once  1 ,, ,, in 5-gr. doses of 0°2 gr.  2 ,, pure amorphous once	23.8 per cent. 27.6 ,, ,, 24.9 ,, ,,	38.5 per cent.			

The arithmetical mean of a single dose of quinine of different salts is 25'4 per cent. The variety of quinine salt,

the difference of dose and other conditions have not the influence on the results as was expected. But of most importance is whether quinine is taken on an empty or full stomach. It is found that when quinine is taken on an empty or nearly empty stomach, the quantity of quinine excreted is as follows:—

```
      Kleine
      ...
      ...
      21'91 per cent.

      Mariani
      ...
      ...
      24'70
      ,,

      Flamini
      ...
      ...
      24'60
      ,,

      Schmitz
      ...
      ...
      ...
      19'50
      ,,

      Giemsa and Schamanes
      ...
      25'80
      ,,
```

The whole quantity excreted by the kidneys, when quinine is taken on an empty stomach, is on the average as follows:—

```
Mariani ... ... ... 40.88 per cent. Flamini ... ... ... 41.00 ,, Schmitz (48 hours) ... ... ... 28.70 ,, Giemsa and Schamanes (72 hours) ... 38.50 ,,
```

When quinine is not repeated daily, analysis of quinine excreted with urine shows about 40 per cent., and the destroyed portion of quinine is about 60 per cent. When quinine is given continuously in medium-sized doses the portion which gets destroyed in the system is considerably more.

For how long after the administration of quinine by the mouth is it excreted? Mariani says up to the sixteenth day, though only a trace. Flamini found that by use of quinine tannate urine contains quinine up to the fifteenth day. With Drs. Giemsa and Schamanes, using I grain quinine hydrochlorate on empty stomach, quinine was not demonstrated with certainty on the thirteenth day. When amorphous quinine is used on full stomach quinine can be detected by pot. mer. silver iodide up to the fifteenth day.

Other ways of quinine excretion have been found in mother's milk, in tears, in transudations and exudations of cellular tissues of the skin, in amniotic fluid, in the urine of the newborn when mother is getting quinine. According to Lewin and Lepidichiat quinine is not excreted by the salivary glands. Some have found quinine in the sweat secretion, and others have failed to find it, and Giemsa and Schamanes failed to find it in their experiments.

THE SPECIAL FACTOR INFLUENCING ABSORPTION AND EXCRETION OF QUININE.—Of the factors specially acting on the excretion of quinine in the urine, which is dependent on absorption, the most important is the condition of the stomach in relation to food. These factors comprise two things: (1) More or less quick absorption of quinine which influences the excretion in the urine in the same degree; and (2) destruction of the alkaloid in the system, which accounts for a large fraction of the quinine.

Recent observers have found that a full stomach delays the excretion of quinine. (Kleine and Mariani.)

Mariani found the following average when quinine was introduced by the mouth:—

Excreted with	In Full Stomach			IN EMPTY STOMACH		
the Urine	Easily soluble	With difficulty soluble	Average	Easily soluble	With difficulty soluble	Average
In first six hours In second ditto	per cent. 7.88 15.77	per cent. 12.01 19.61	per cent. 9'95 17'69	per cent. 17.37 10.86	per cent. 13'41 12'30	per cent. 15.39 11.58
Total	44*45	68.43	56.44	36.48	45.20	40°35

Here the relation of the excretion co-efficient to the administered quinine for full and empty stomach in the first twenty-four hours is 37.03:27.95 and total 56.44:40.88.

According to Giemsa and Schamanes the excretion of quinine taken during meal-time takes place as follows:—

First day	0 5-0	1,500 c.n	. urine excretion		22.7 per cen	it.
Second day		2,200 ,,	33	•••	12.3 ,,	
Third day	•••	1,600 ,,	23		4.8 ,,	
In three day	- s	5,300 ,,	excreted		39.8 ,,	

Thus, while the observers found 39.8 per cent. quinine here, after seventy-two hours Mariani found as high an average as 68.43 per cent. A full stomach hinders quinine absorption, and the distinct quinine reaction with pot. merc. iodid. is found in such cases in about two hours, whilst in empty stomachs the quinine is detected, as a rule, within twenty to thirty minutes.

The same observers found that the average excretion of quinine in the urine is 23.8 per cent. of the quantity administered when given in one dose, and 27.8 per cent. when given in divided doses of 0.2 gramme in ten hours.

The view that the preparation of quinine which is easily soluble in water is the more easily absorbed is the most accepted one. These observers found that the salt which is with difficulty soluble in water is at least as energetically absorbed by the mucous membrane of the stomach as is the easily soluble salt.

Quinine Accumulation.—On comparing the results of several observers the average excretion of continual administration of quinine is 21'1 per cent. more than that in the case of intermittent administration.

Brignet and Quivenne found the total excretion in continual treatment with same daily dose of quinine to be 52.3 per cent.; Mariani, 34.52 per cent., and Drs. Giemsa and Schamanes, 25.8 per cent.

In dogs treated with large doses of quinine the amount found circulating in the blood was very small, and examination of organs showed that very small quantities indeed were stored up and that it disappeared very rapidly. There is no reason to believe it is different in the human being. After forty-eight hours quinine is excreted in very small quantities, and in seventy-two hours cannot be detected by the most delicate test. This falling of the amount excreted is due to increased destruction of quinine. Kleine and Schmitz have pointed out that the longer quinine is administered the power of the human organ to break up quinine is not increased, as has been shown by Mariani, but that by repeated daily administration of quinine some portion is stored up in the blood. According to Giemsa and Schamanes the human cell can under certain conditions destroy quinine in large quantities. This not only explains the deficiency o quinine excretion in continuous quinine treatment, but also the excretion of the alkaloid varied daily in continued treatment, as compared with divided dose treatment owing to greater destruction in the former. Therefore it would seem the divided dose is the better treatment. This is also the opinion of Bif Nocht and Drufer.

Quinine Salt and Blackwater Fever. — Some have thought that blackwater fever is caused solely by quinine, and that the alkaloid is absorbed and excreted in some abnormal manner in certain predisposed persons, or that in those cases there was some combination between the quinine and hæmoglobin. Marchoux found that quinine was not excreted during hæmoglobinuria, but was excreted in large quantities when the urine returned to its normal colour, thus suggesting that the quinine was stored up in the blood, and reached such a high degree that it caused the hæmolysis. Many have written against this view, and we know that hæmoglobinuria is often caused by a single dose of a relatively small quantity of quinine, and that it is also caused by other drugs.

Drs. Grange and Schamanes observed ten cases carefully. The attacks came on when the persons were under observation with quinine treatment. The results of these cases are given in Table I.

In six the whole urine was quantitatively examined for quinine from the start of the hæmoglobinuria. In three (4, 5 and 8) the examination for alkaloid excretion was from the beginning, before the onset.

In one case the hæmoglominuria started after one administration of 8 grains (Table II.); in nine cases after one, two or several doses of I grain of quinine. In Cases 4, 5 and 8 the best administration was during the hæmoglobin fever period. In one case the patient had I grain quinine in five doses of 0.2 grain in the course of ten hours. This was tolerated for eighteen days; then in the evening of ninth day (= I day of table) a weak hæmoglobinuria set in and the quinine was stopped. The urine of first day of attack was not collected, and hence relatively small quantity of quinine found. These results are against the views of Marchoux, as the alkaloid was excreted both during and after the hæmoglobinuria. In comparison to the normal percentage the alkaloid excretion seems to these observers to have a larger percentage. Lemiel also found quinine excreted during hæmoglobinuria. They find no explanation in the source of hæmoglobin in the excretion of quinine in blackwater fever. The finding of a large quantity of quinine which is excreted during blackwater fever makes these observers conclude that the disease is not caused by the action of some poisonous element of quinine separating from it by the action of the organism.

TABLE I.

ONE GRAIN OF QUININE MURIATE TAKEN DAILY BY MOUTH.

OI		1		l	I	1	
6		Not examined	22.0*	8.1	Not examined	•	
80		24.8	$\left\{\begin{array}{c} 2.9\\19.1^{*}\end{array}\right\}$	6.01	3.0	•	35.6
7		Not examined	*8.61	*1.6	4.5	:	33.1
9	in per cent.	Not examined	21.5*	9. 9.	Trace	:	32.8
۱۷	Excreted quinine in per cent.	5.2.2	8.4	6.5	4.5	:	30.6
4	<u>원</u>	5.8.5	4.5	4.7		Trace	39.0
ю		Not examined	19.2*	Not (	2.5	•	
6		Not examined	18.5*	Not examined 6	:	•	 
ы		Not examined	*61	5.27	3.2	:	34.9
No. of case:		In the course of previous 24 hours the dose of quinine which caused	1st day	znd day	3rd day	4th day	Total excretion after last dose of quinine in per cent.

TABLE II.

ONE CASE, 8 GRAINS QUININE MURIATE BY MOUTH.

	Days: I	Days: I	Days: I	Days: I
Days:	Days:	Days:	Days:	Days:
Days:	Days:	Days:	Days:	Days:
:				
	cent.	per cent.	in per cent.	quinine in per cent.

Note.—Twenty-four hours intervened between each administration of quinine. Those with \* give result of quinine in the urine while the hæmoglobinuria was on, those without \* are from hæmoglobin-free urine.

TABLE III. Quinine and Quinine Preparations.

Quinine	1	1	0.320 gr.	48 cc.	
Quinine carbon	Ch,H,CO,+H,O	547	o.591 gr.	I c.cm.	
Quinine bisulphate	Ch <sub>2</sub> H <sub>4</sub> SO <sub>4</sub> +7H <sub>2</sub> O	548	0.591 gr.	9 c.cm.	
Quinine sulphate	Ch2H2SO4+8H3O	890	0.728 gr.	800 c.cm.	
Quinine bimuriate	Ch <sub>2</sub> HCh	397	0.816gr.	ı c.cm.	
Quinine muriate	ChHCl+2H2O	3.96.2	o.816 gr.	34 c.cm.	
Quinine base, market	Ch + 3H20	378	0.851 gr.	1428 cm.	
Quinine base, water free	$C_{20}H_{24}N_{2}O_{2}$	324	1.0005 gr.	:	
Name of the corresponding quinine preparation	Chemical formula   C20H24N2O2   Ch+3H2O   ChHCl+2H2O   Ch2HCh   Ch2H2SO4+8H3O   Ch2H2SO4+7H2O   Ch2H3CO2+H3O	Molecular weight	I gr. contains free base	Solubility of 1 gr. in cc. of water at 20°	

#### APPENDIX J.

TESTS FOR BILE IN THE URINE.

A. For Bile Pigments.

(1) Ocular Evidence.—When in any quantity its presence can be recognized by the eye. Also when testing for albumin by

nitric acid a peculiar greenish reaction results.

(2) Gmelin's "Contact Method."—A "green ring" is obtained on adding nitric acid to urine by the "contact method." This test is also applied by placing a few drops of urine and a few drops of nitric acid on a white plate and allowing them to run into each other, when a play of colours is observed (green, blue, violet, red and dirty yellow) which quickly fades away. (Dilution of the nitric acid with three volumes of water favours distinctness of reaction).

(N.B.—Rhubarb, santonin and senna with HNO<sub>3</sub> give a colour reaction like that of bile; to distinguish them from bile

add KHO, when they give a red colour).1

(3) Maréchal's Iodine Test.—(Tincture iodine one part, rect. spt. two parts.) On to some urine in a test-tube pour, by means of a pipette, two or three drops of this diluted tincture of iodine. A green band is developed at the juncture of the the fluids. (Too much tincture of iodine may obscure the green colour. If the urine is very highly coloured it should be diluted with water beforehand.)

(4) Obermayer and Popper's Test (Wien. klin. Woch.). — Reagent used: Potassium iodide, 12 grammes; sodium chloride, 75 grammes; 10 per cent. tincture of iodine,  $3\frac{1}{2}$  cc.; 95 per cent. alcohol,  $12\frac{1}{2}$  cc.; distilled water, 625 cc. Three or four cubic centimetres of the reagent are placed in a test-tube and 5 cc. of fresh urine are run on to it, so that a sharp contact surface is formed. (Highly coloured urine must be diluted first.) When much bile is present a dark bluish-green ring is formed; when less is present a pure green ring; and with

Agitate the red colour with amyl alcohol, when the colour due to the santonin passes into the alcohol, which in contact with the air changes into yellow; the colour due to chrysophanic acid in rhubarb does not dissolve in alcohol or only in minute traces.

slight traces a blue ring. It is a simple and a scientific test and is said to detect very small quantities of bile in the urine.

- (5) Krokiewicz's Test (Munch. med. Wochenschr., October, 1906).

  —Take five drops each of a 1 per cent. aqueous solution. of sulphanilic acid and 1 per cent. sodium nitrite solution; mix in a test-tube with an equal bulk of the urine to be tested. If bile pigments be present the mixture assumes a ruby-red colour, which, on the addition of a few drops of hydrochloric acid and dilution with distilled water changes to an amethyst violet.<sup>1</sup>
  - (6) Spectroscope.
  - B. For BILE ACIDS.

Tests for bile acids and salts are said to be unreliable.

- (1) Pettenkofer's.—To 5 cc. urine add a few crystals of sugar; shake. By means of a pipette add strong sulphuric acid to the bottom of the urine in the test-tube. A purple ring at the junction is regarded as positive evidence.
- (2) Dr. Oliver's test by means of an antiseptic solution of artificial peptones. (For details and precautions see Dr. Oliver's work.)

#### THE VARIOUS BILE PIGMENTS.

- Bilirubin (C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>).
   Biliverdin (C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>).
- (3) Choletelin (C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>).
- (4) Bilifuscin ( $C_{16}H_{20}N_4O_7$ ). (5) Biliprasin ( $C_{16}H_{22}N_2O_6$ ).
- (6) Hydrobilirubin  $(C_{33}H_{44}N_4O_7)$ .

The parent of most of the various pigments of the body is in all probability the pigment of the blood, the hæmoglobin. One of the characteristic properties of pigments is that when white light is passed through a solution of the pigment and then through a prism, part of the light is absorbed so that certain "bands" appear in the spectrum, termed "absorption bands," hence the value of the spectroscope for research and diagnostic purposes. (For further details re spectroscope see MacMunn, "The Spectroscope in Medicine.")

<sup>&</sup>lt;sup>1</sup> If this test is applied for bile in gastric contents the addition of HCl is usually unnecessary owing to the acid gastric juice.

(1) Bilirubin on oxidation is changed into biliverdin and choletelin, and during oxidation other transitory bodies are formed. On this fact depends Gmelin's test. If biliverdin alone is present the play of colours begins with the blue. A solution that shows Gmelin's reaction, when examined spectroscopically, gives "a broad shading (probably composed of two distinct bands) in orange and yellow, and a black band extending from near b to beyond F. . . . In a very short time the shading in orange begins to fade, and at the time the oxidation is completed and the colour of the solution has become yellow, nothing but the band at F is left." (MacMunn, "The Spectroscope in Medicine," p. 160.)

As the direct injection of a solution of hæmoglobin into the blood does not cause an increase of urinary pigment (McKendrick's "Physiology"), and since chemists have never artifically obtained bilirubin from the decomposition of hæmoglobin, it would appear to the author that any presence or increase of such pigment in blackwater fever is due either to the circulation in the blood of such pigment, or as a product in an imperfectly formed state, but which by oxidation in the urine becomes bilirubin. (Disqué says there is a colourless form of urobilin which may be called "reduced urobilin" or

"chromogen," which gives no absorption band.)

(2) The normal *urobilin* is regarded by MacMunn as an oxidation product of effete hæmatin and bile pigments. It is significant that urobilin can be obtained from hæmoglobin and hæmatin and from bilirubin by *reducing* agents, and that when blood has been extravasated in large quantities into the tissues the urobilin of the urine is much increased. In acid solution it gives an absorption band close to and including Fraunhofer's line F in the spectrum. With chloride of zinc and ammonia it gives a rose-coloured solution with green fluorescence, and a narrower and fainter band to the left of F and less of the blue is visible.

(3) Biliverdin is obtained from the oxidation of bilirubin; and

(4) Choletelin is an oxidation product of biliverdin. This latter does not give Ginelin's reaction, having been oxidized past that stage, and neither does bilifuscin. The whole subject of bile pigments and their presence in the urine in disease requires fuller investigation.

#### APPENDIX K.

#### PREVENTION OF BLACKWATER FEVER.

The prevention of blackwater fever, or bilious malignant tertian ague, means the prevention of malaria. Briefly summed up, this means the following measures:—

- (A) Personal Measures—those which the individual must undertake to protect himself. They are:—
  - (a) Mechanical:-
    - (1) Mosquito nets to beds.
    - (2) Wire gauze screens to doors, windows, and on verandahs (mesh 20 to the inch).
    - (3) Nets over face (used by Italians on railways in malarial districts).
    - (4) Gloves, gaiters, leggings.
    - (5) Fans.
  - (b) Medicinal:-
    - (1) Quininization. Daily dose of quinine of 10 grains, in two doses of 5 grains, taken night and morning from June to December; and 5 grains daily, or 10 grains every fourth day and last day of month, between January and end of May.
    - (2) Use of magnesium sulphate or soda sulphate occasionally to keep liver free from congestion.
    - (3) Use of insecticides, such as pyrethrum and sulphur, to destroy mosquitoes.
    - (4) Local applications of oils and pomades, such as cocoanut oil, kerosene oil, citronella oil, eucalyptus oil, &c.¹

<sup>&</sup>lt;sup>1</sup> A mixture of citronella, kerosene and cocoanut oils, with a certain proportion of carbolic acid, makes a most useful mixture in which the objectionable odours of kerosene and cocoanut oils is completely disguised. It is a limpid liquid, smelling only of citronella, the effect of which is more lasting. Coolies will have no objection to it, and it can be made at a cost of Rs. 4.50 a gallon. An ordinary kerosene oil tin holds four gallons, and, allowing for wastage, this would give 4,000 coolies a single application. Thus the cost is infinitesimal compared to the benefits to be derived.

(c) Sanitary:-

- (1) Stone or brick houses built with a well-raised plinth.<sup>1</sup>
- (2) Good drainage.
- (3) Absence of all jungle around house.
- (4) Absence of all unnecessary trees around house which keep out breeze and harbour mosquitoes, and especially the destruction of all plantain and bamboo trees, which often breed mosquitoes in collections of water thereon in branchings or cut surfaces.
- (5) The use of kerosene oil to any collections of water within a mile radius of the house.
- (6) All rain gutters of house should especially be seen to have a correct fall, and no unevenness permitting water collection.
- (7) No collections of rubbish permitted near any dwelling.
- (8) All other measures advised by the medical officer should be carried out.<sup>2</sup>

<sup>&</sup>lt;sup>1</sup> The coolies usually live in hovels—small, dark, damp, dirty, smoky, ill-ventilated huts of bamboo and thatch. Around there is no drainage, and usually a collection of filth made up of débris of all kinds, manure (animal and human), collections of water, garbage and jungle. Usually either cattle or goats are kept in immediate relationship to the dwelling. Under such conditions coolies, who are none too well fed or clothed, are expected to keep fit to do the hard work on the estates in a trying climate under all meteorological conditions! No attempt is made to save the lives of coolies by preventive means! Is there any need for surprise that labour is not sufficient for the demand? If coolies were better housed in brick houses on a well-raised plinth, with sanitary surroundings (under supervision of one man to a given number of lines), and wire gauze windows and doors to their houses, combined with quininization, they would then have some chance of withstanding malaria and keeping in good health. This would pay all estates. The brick houses could be built so many a year, and would not be expensive. They would last longer than the huts, and would be a valuable asset to the estate. Coolies will appreciate good houses as well as anyone, and the example of the mills outside Calcutta is sufficient evidence to show that all classes of labour will go into them.

<sup>&</sup>lt;sup>2</sup> The local medical officer knows best what is necessary. His advice should, in all these matters, be sought and carried out. The medical officer should be appointed directly by the agents, and all medical and sanitary matters concerning the estate in any way should be referred to him, and until this is done complete and satisfactory medical and sanitary measures will never be carried out.

- (B) Public Measures—to be carried out partly by State municipalities, societies, and those in control of labour:—
  - (1) Wholesale and free administration of quinine to every man, woman and child in a malarial area. This can easily be carried out where labour is under control, e.g., at mills and tea estates. The quinine should be administered by pills (fresh) every morning at muster under European supervision.
  - (2) Wire gauze to windows and doors of dwellings; this should be made compulsory. Coolie houses should be improved, and they should have such to their houses.
  - (3) Segregation of affected individuals, though advisable, is not at present practicable.
  - (4) Destruction of mosquito larvæ by drainage and accessory means.



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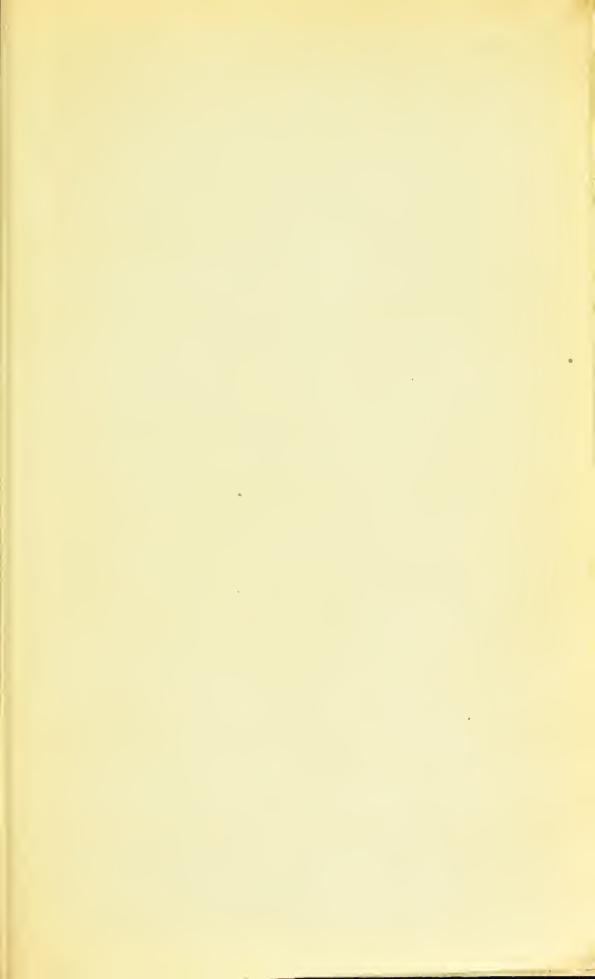
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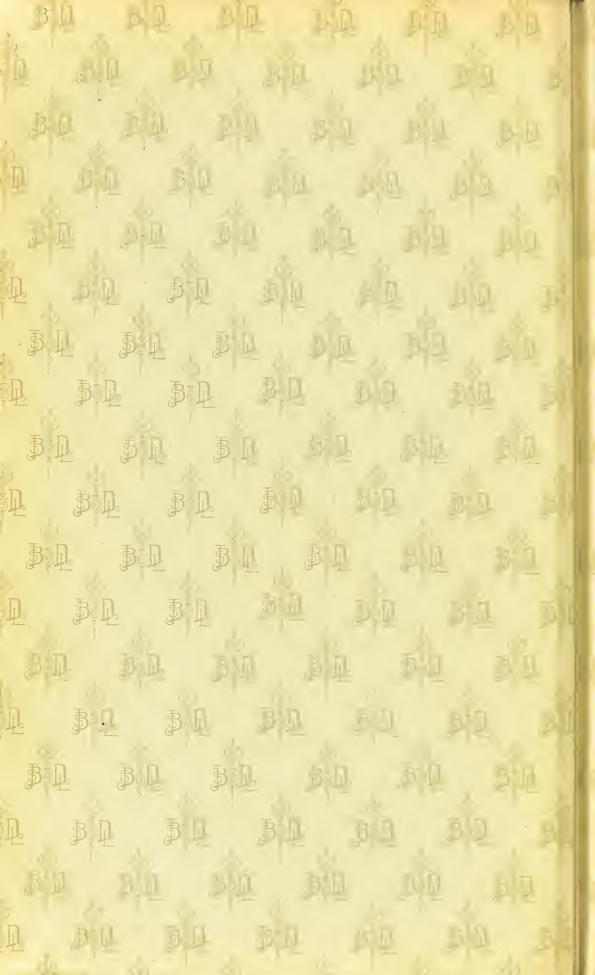
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